Clinical Approaches and Procedures in Cosmetic Dermatology

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Daily Routine in Cosmetic Dermatology

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Clinical Approaches and Procedures in Cosmetic Dermatology

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The series “Clinical Approach and Procedures in Cosmetic Dermatology” intends to be a practical guide in Cosmetic Dermatology. Procedures in cosmetic dermatology are very popular and useful in medicine, indicated to complement topical and oral treatments not only for photodamaged skin but also for other dermatosis such as acne, rosacea, scars, etc. Also, full-face treatments using peelings, lasers, fillers and toxins are increasingly being used, successfully substituting or postponing the need for plastic surgeries. Altogether, these techniques not only provide immediate results but also help patients to sustain long-term benefits, both preventing/treating dermatological diseases and maintaining a healthy and youthful skin. Throughout this series, different treatments in Cosmetic Dermatology will be discussed in detail covering the use of many pharmacological groups of cosmeceuticals, the new advances in nutraceuticals and emerging technologies and procedures.

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With 132 Figures and 46 Tables

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Foreword

When I received the invitation from Maria Claudia Almeida Issa, M.D., Ph.D., and Bhertha Tamura, M.D., Ph.D., to write one of the chapters of this marvelous book, I was very happy. Later, upon receiving the mission to write the prologue of this book whose editors, with numerous publications in the international scientific field of cosmetic dermatology, dignify the Brazilian dermatology left me extremely honored. In this book, some of the leading medical doctors and research scientists from Brazil and from all over the world present their professional experience in the cosmetic dermatology area.

Cosmetic dermatology is constantly evolving. Procedures for rejuvenating the skin are actively sought by people, nowadays. As dermatology grows as a specialty, an increasing proportion of dermatologists will become proficient in the delivery of different procedures. Even those who do not perform cosmetic procedures must be well versed in the details to be able to guide their patients.

Numerous major advances in the field of the cosmetic dermatology area, including botulinum toxin, soft tissue augmentation, chemical peels, cutaneous lasers, light source-based procedures, and the state of the art of dermatologic and cosmetic prescriptions, have been developed and enhanced by dermatologists.

This series of book begins by demonstrating skin histology and physiology of normal skin and discusses important topics as anamnesis, physical and psychological approach in cosmetic dermatology, topical and oral treatment, as well as procedures in cosmetic dermatology.

The series Clinical Approach and Procedures in Cosmetic Dermatology offers a wonderful and embracing text. It was a pleasure to contribute in this unique book with so many well-renowned authors.

This work project is a text certainly of inestimable value for those who wish to deepen their knowledge in the field of cosmetic dermatology.

Hoping that you will enjoy learning a lot from this book!

Mônica Manela Azulay

Preface

Nowadays, life expectation had increased and for a better quality of life, people are looking for beauty, aesthetics, and health. Dermatologists and plastic surgeons who work with cosmetic dermatology can help patients to maintain a healthy and youthful skin. Topical and oral treatments associated with full-face procedures using peelings, lasers, fillers, and toxins are increasingly being used, successfully substituting or postponing the need for plastic surgeries.

This series of book is very special among other ones already published as it encompasses all subjects related to this area of dermatology. All authors are experts in the field of cosmetic dermatology. Literature review and its correlation with authors' experience is a differential feature of this work.

This work had been divided into four volumes due to the breadth of the subjects, which cover skin anatomy and histopathology, physiology, patient's approaches, common cosmetic dermatosis, topical and oral treatments, and cosmetic procedures.

In *Daily Routine in Cosmetic Dermatology*, Prof. Maria Claudia Almeida Issa, Prof. Bhertha Tamura, and collaborators provide a complete summary of cosmetic dermatology. Here they describe with details the daily routine in this field, including careful approach of the cosmetic patients and the proper handling of topical and oral photoprotection, cosmeceuticals, and nutraceuticals. Classic and emerging procedures are also covered in this volume, but they are going to be deeply delineated in further volumes.

The *Clinical Approach and Procedures in Cosmetic Dermatology* was prepared to be a guide in cosmetic dermatology. It can be considered a complete encyclopedia in the field of cosmetic dermatology and, for this reason, it is extremely useful for those who already work with cosmetic dermatology as well as for beginners in this field. This is a new reference work project, and we are delighted to have you on board.

Maria Claudia Almeida Issa
Bhertha Tamura

Acknowledgments

When we were invited to write a book about cosmetic dermatology, we could not imagine the dimension of this work project.

After drawing the program content, we realized that a comprehensive handbook series in this field would be built. Nevertheless, it would not be possible without the efforts and experience of our invited partners. They deserve our acknowledgment and our deep appreciation.

To all collaborators, our very special thanks.

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About the Editors

Maria Claudia Almeida Issa is among the leading dermatologists in Brazil and Latin America, especially in what regards to cosmetic dermatology. Dr. Issa holds a Ph.D. in Dermatology from the Federal University of Rio de Janeiro (2008) and an M.Sc. in Dermatology from the Fluminense Federal University (1997). Dr. Issa is currently an Associate Professor within the Department of Clinical Medicine – Dermatology, at the Fluminense Federal University, Brazil. Her research focuses on photodynamic therapy, non-melanoma skin cancer, lasers, photoaging, and dermal remodeling. Finally, Dr. Issa has an extensive clinical experience in cosmetic dermatology, being registered as a dermatologist at the Brazilian Society of Dermatology since 1995 and member of the American Academy of Dermatology.

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Part I

Normal Skin

Skin Anatomy, Histology, and Physiology

Camila Sampaio Ribeiro, Fabiano Leal, and Thiago Jeunon

Abstract

Increasingly, patients are requesting information and treatments to ameliorate the effects of skin aging. Skin aging is a biological process determinated by endogenous and exogenous factors. Cosmetic interventions may have a significant impact on the health and well-being of patients. Over the last years, several antiaging strategies have been developed, and doctors must be up to date with these constant advances. Interventions, for the facial aging mainly, may be categorized into four "Rs" of facial rejuvenation: *resurfacing* (chemical peels, dermabrasion, microneedling, and ablative and non-ablative lasers), *redraping* (the various pulling and lifting facial surgical procedures), *relaxing* (chemodenervation with paralytic agents), and *replacement/recontouring* (the use of filling agent for superficial and deep soft tissue augmentation). However, before delving into the techniques to perform cosmetic procedures, it is essential to have full knowledge of the histology, physiology, and topographic particularities of the skin. This first chapter is also the first and essential step for the construction of your knowledge on cosmetic procedures. So, make sure you understand every detail before you move forward.

Keywords

Anatomy • Histology • Physiology • Skin

Contents

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Introduction

The skin is a vital organ for human life. It plays a complex set of functions and is essential for maintaining homeostasis. It covers the entire body surface providing the major site of interaction with the surrounding environment. The skin's most important function is to maintain the hydric balance of the organism and form an effective mechanical barrier against external injury whether physical, chemical, or biological. Apart from protection, the skin actively participates in thermoregulation and it is involved in the immunological surveillance. It plays a critical role in the synthesis of vitamin D and functions as a sensory organ in detecting different stimuli (Ackerman 1997; Proksch et al. 2008; Blank 1965).

The skin's health is determinant in social relationships. A compromised skin integrity results in a relevant psychological and social impact in people's lives harming communication among individuals.

Cutaneous aging involves an intrinsic chronological process and also an extrinsic process due to environmental factors, especially sun exposure (Fig. 1a, b). A significant portion of the population is overly exposed to sunlight during labor and/or recreation activities. Damage of the ozone layer is an aggravating factor that contributes to earlier occurrence of signs of photodamaged skin on current population. At the microscopic level, a relevant feature of photoaging is the accumulation of solar elastosis in the upper and middle dermis. Avoidance of excessive sun exposure is still the most recommended strategy to prevent cutaneous photoaging.

Moreover, the population is living longer and patients are seeking for low-risk cosmetic procedures with associated minimal downtime. Great advances have appeared in response to the aesthetic claims for treatments that will "turn back the clock" and make people look and feel younger.

The purpose of this chapter is to discuss the skin's histology, physiology, and topographic particularities emphasizing on its important points for executing some cosmetic procedures. This step, along with the complete understanding of the mechanisms of action of established aesthetic treatments, is essential for safety and efficacy of these treatments.

The Epidermis

The structure of the skin consists of two layers: the epidermis and the dermis. The epidermis is the outermost layer of the integument. It is composed of stratified keratinized squamous epithelial tissue.

It is an avascular tissue that consists of four layers of keratinocytes in their various stages of differentiation. From the deepest layer to the more superficial, they are the basal cell layer, the spinous or squamous layer, the granular cell layer,

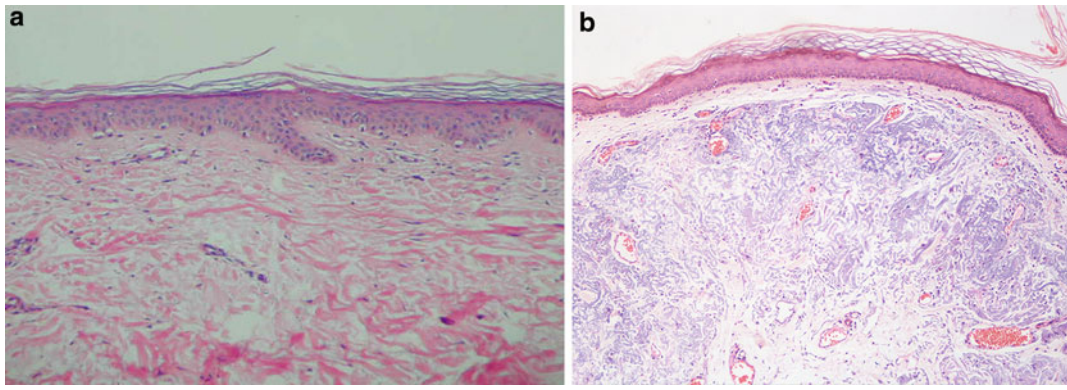

Fig. 1 Eldery skin. (**a**) Elderly skin in an area unexposed to sunlight. Note that the epidermis is thin, with a flattened base, but there is no solar elastosis in the dermis. H&E, 100x. (**b**) Elderly skin in an area exposed to sunlight. Note that there are numerous basophilic fibers in the dermis named solar elastosis. HE, 100x

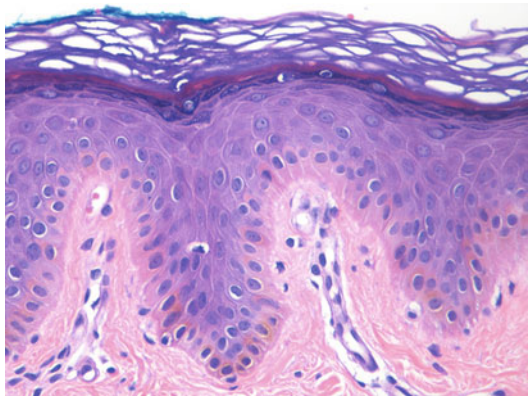

Fig. 2 Epidermis. The epidermis is a stratified keratinized epithelium. The nucleated portion is composed by the basal cell layer, squamous cell layer, and granular cell layer, which are referred collectively as Malpighian layer. The stratum corneum is anucleated and composed by dead cells. (HE, 200x)

and the stratum corneum. The first three compose the nucleated portion of the epidermis and are referred collectively as Malpighian layer. The stratum corneum is composed by completely keratinized cells that are no longer alive but still play an important role in the homeostasis of the epidermis (Fig. 2).

The interface between the two layers of the skin is known as the dermal-epidermal junction. It is an extremely complex structure and it is essential to life. The primary function of the basement membrane is to promote adherence of the epidermis to the dermis, keeping the permeability required for the diffusion of nutrients and oxygen. The basement membrane is not visualized in sections of tissue stained by hematoxylin and eosine, but it is seen as a thin line under the keratinocytes of the basal layer when Periodic acid of Schiff stain is applied.

Keratinocytes of the *basal layer* are the least differentiated cells of the epidermis and form a single row of columnar cells with the major axis perpendicular with the dermoepidermal junction. They are the only keratinocytes of the epidermis with reproductive ability, functioning as cell reservoir and supplying continuously, through cell division, keratinocytes to higher layers (stratum spinosum, stratum granulosum, and stratum corneum).

Depending on the body's anatomical area, Malpighian layer thickness varies. In general, the thickness of the epidermis varies from 0.04 mm on the eyelids to 1.6 mm on the palms and soles of the feet. The *spinous layer* is composed by larger keratinocytes than the basal cells, with a polyhedric shape, and they may be arranged in five to ten layers of cells.

The *granular layer* has three rows of cells in the thin skin and is composed of large flattened cells, with a rhomboid shape and major axis parallel to the epidermis surface. Their cytoplasm is filled with keratohyalin granules that are quite basophilic. The keratohyalin granules contain substances such as pro-filaggrin (which is converted in filaggrin that functions as an adhesive promoting adhesion of keratin filaments to form thicker filaments) and loricrin (which contributes to the formation of an insoluble intracytoplasmic barrier known as cell envelope). The granulocytes also contain small lipid laminated granules known as Odland bodies. They are secreted to the extracellular environment during the keratinization process and contribute to maintain the stability, impermeability, and lubrication of the stratum corneum (Ackerman 1997; Bolognia et al. n.d.; Calonje et al. 2011; Goldsmith et al. 2012; Lever and Elder 2005).

The *stratum corneum* consists of fully differentiated and keratinized anucleated keratinocytes. Corneocytes are embedded in intercellular matrix composed of cholesterol, free fatty acids, and glucosylceramides. This structure is essential for the stratum corneum to keep the skin's adequate moisture and simultaneously preserve the hydric barrier. Ambient humidity and temperature are also important to determinate the moisture level of the skin because they influence in water retention and in the degree of evaporation through the corneal layer. Also, aging and ultraviolet radiation are among the many other stressors to the skin that decrease skin barrier function and increase transepidermal water loss (Blank 1965; Madison 2003).

The skin thickness and hydration of different body parts vary, and these aspects are determinant on the decision of the most adequate cosmetic procedure to be performed. Skin thickness depends on both the epidermis and the dermis

thickness, which, as aforementioned, varies at different anatomical sites of the body. Hydration depends primarily on epidermis thickness and on the presence of cutaneous appendages.

The epidermis exists in a dynamic state. Keratinocytes constantly divide and migrate upward from the basal cell layer toward the stratum corneum, in a vertically oriented path. As keratinocytes migrate, they progressively differentiate until complete keratinization at the stratum corneum. The maturation process of an undifferentiated basal cell to become a corneocyte lasts about 14 days. And, also, a corneocyte takes about 14 additional days to peel off the skin surface. Thus, in normal conditions, the epidermis, with the exception of cells that remained in the basal layer, is completely renewed every 4 weeks.

Besides keratinocytes, the epidermis also houses melanocytes, Langerhans cells, Merkel cells, and undifferentiated cells (Ackerman 1997; Bolognia et al. n.d.; Calonje et al. 2011; Goldsmith et al. 2012; Lever and Elder 2005).

Other Cells of the Epidermis

Melanocytes are non-epithelial cells derived from the neural crest that produce melanin. They are distributed equidistantly along the basal layer on the average of one melanocyte for every ten basal keratinocytes. In vivo, melanocytes have dendritic cytoplasmic processes that enable melanocytes to transfer the melanin to the cytoplasm of keratinocytes.

Melanin is a brown pigment that is synthesized by melanocytes inside intracytoplasmic structures called melanosomes.

Melanin synthesis, a process named melanogenesis, is characterized by four stages of maturation along with melanosomes that become gradually pigmented. The melanosomes migrate through the cytoplasmic dendritic processes inside melanocytes to be transferred to the cytoplasm of keratinocytes. The pigment predominates in the lower layers of the epidermis, especially in the basal cells. Ultraviolet radiation is the most important extrinsic factor in the regulation of melanogenesis.

The number of melanocytes does not vary between individuals of different skin colors; it is relatively constant among all ethnic groups. Phenotypic diversity of cutaneous pigmentation relies on the amount of melanin and the size and distribution of the melanosomes in the cytoplasm of keratinocytes.

Two types of melanin are synthesized within melanosomes: eumelanin and pheomelanin. Eumelanin is predominantly found in individuals with dark skin and hair, whereas pheomelanin is the major type in individuals with red hair and skin phototypes I and II.

In light-skinned people, melanosomes are smaller, mainly at early stages I and II of maturation, and they are transferred to the neighboring cells as clusters in membrane-bound organelles.

On the other hand, in darkly pigmented skin, melanosomes are more abundant, larger, at stage IV, and singly transferred to the surrounding keratinocytes. Their degradation appears also slower than that observed in light skin. And they are more efficient in photoprotection.

Melanogenesis involves specialized enzymes localized within melanosomes, such as tyrosinase and tyrosinase-related ones. Tyrosinase is a copper-dependent enzyme that catalyzes the conversion of L-tyrosine into L-DOPA, the rate-limiting stage in melanin synthesis.

Pigmentary disorders are a group of skin diseases that include hyperpigmentation (melasma, café au lait spot, postinflammatory hyperpigmentation, and solar lentigo) and hypopigmentation (postinflammatory hypopigmentation, vitiligo, idiopathic guttate hypomelanosis) imperfections.

One of the most common pigmentation disorders involving the face is melasma. It is an acquired hyperpigmentation condition, and its major etiological factors include chronic exposure to ultraviolet radiation and female sex hormones (pregnancy and oral contraception).

Melasma may be classified, according to the location of the pigment, as epidermal, dermal, or mixed type. Epidermal melasma is characterized by increased deposition of melanin in epidermal keratinocytes (predominantly in the basal and suprabasal layers) possibly due to increased activity of melanogenic enzymes and

by an increased number of melanocytes. In the dermal type, the epidermal findings are also seen, associated with the presence of increased melanin in macrophages in the superficial dermis. Besides that, changes from chronic sun exposure are frequently observed: solar elastosis and findings in dermal microvasculature with a greater density of blood vessels with twisted dilated aspect.

The management of melasma is usually challenging. It is often recalcitrant to treatment and recurring despite successful treatment. The regulation of melanogenesis is crucial for an effective treatment. Numerous pigment-lightening agents have been developed. These agents have different mechanisms of action: influence in tyrosinase activity and/or stability, melanosome maturation, transfer and trafficking, or in melanogenesis-related signaling pathways.

Hydroquinone (HQ) is the most popular antimelanogenic agent. HQ is a competitive inhibitor of tyrosinase, the rate-limiting enzyme in melanogenesis. It inhibits the conversion of l-3,4-dihydroxyphenylalanine to melanin. Hydroquinone may be combined with AHAs, retinol, vitamin C, and topical steroids. Kojic acid and arbutin also act through tyrosinase inhibition leading to reduction in melanin synthesis. Nicotinamide impacts in the transfer of melanin from melanocytes to keratinocytes. Retinoic acid acts as a modulator of epidermal differentiation, speeding desquamation and removing excessive melanin content within the epidermis. Azelaic acid, a compound widely used in Brazil, prevents tyrosine to bind in the active site of tyrosinase by binding of amino and carboxyl groups, i.e., acting as a competitive inhibitor.

Langerhans cells are dendritic cells that reside between keratinocytes at squamous layer of the epidermis. They play an important role in immune homeostasis. Free nerve endings present in the epidermis seem to be in touch to Langerhans cells, suggesting a connection between the immune and neurologic systems. In routine stains, Langerhans cells are usually unnoticed (Ackerman 1997; Bolognia et al. n.d.; Calonje et al. 2011; Goldsmith et al. 2012; Lever and Elder 2005).

Merkel cells originate from the skin itself from undifferentiated stem cells. They are present between the basal keratinocytes, and, in routine sections, it is not possible to differentiate them from melanocytes (Ackerman 1997).

Unaesthetic Conditions Involving the Epidermis

Several unaesthetic dermatoses related to chronological and photo-induced cutaneous aging are housed in the epidermis. Among the most prevalent ones are ephelides, solar lentigos, seborrheic keratosis, epidermal melasma, solar keratosis, and porokeratosis. These conditions, alone or occurring concurrently, may have an important impact in the appearance and self-esteem of an individual. In order to have a satisfactory result, it is primordial to have a clear understanding of the dermatosis that is intended to treat. The level of the skin where the lesion is placed and its physiopathology impact on the selection of the treatments to be performed, allowing optimum response with the minimal necessary aggression.

Cosmetic treatments allow partial reversal of those epidermal changes. A good number of dermatologic procedures and medications, such as superficial chemical peels, lasers, intense pulse light (IPL), microneedling, and topical drugs (e.g., Kligman formulation), may be efficient options to treat those epidermal dermatoses and provide patients quality of life as a result of their better look.

Advances in laser technology have been dramatic, and therapeutic applications of lasers are getting broader with a growing number and variety of skin lesions that may be treated with this modality.

Lasers, IPL, or resurfacing machines are either ablative or non-ablative treatments. *Non-ablative* treatments target the lower layers of skin (dermis) while leaving the skin surface (epidermis) unharmed and intact. *Ablative* laser resurfacing targets both the epidermis and the dermis by injuring or "ablating" the surface of skin. Laser therapy is not without risks and the choice of ablative and non-ablative laser depends on downtime and expectations of your patient.

Chemical peels may be an alternative to laser therapy due to low cost. They represent a useful tool in cosmiatry. Depending on the active ingredients, pH, time, and method of application, chemical peels may reach different levels of the skin. Thus, they are divided into three categories depending on the depth reached. *Superficial chemical peels* exfoliate epidermal layers without going beyond the basal layer, while *medium peels* penetrate down to the papillary dermis. *Deep chemical peels* create a wound that reaches the level of the upper part of the reticular dermis. The selection of the right peeling substance depends on the dermatose to be treated, the area of body affected, and the skin color of the patient.

Chemical peels function destroying the cells of the skin, in a controlled manner, and the regeneration process from basal cells and/or from the skin appendages replaces part, or the entire, epidermis and induces histologic changes (a compacted stratum corneum, smoother epidermis, increased dermal thickness with production of elastin and neocollagenesis, and better skin hydration with improved epidermal barrier function). These changes reflect on the skin appearance and help to improve pore size, superficial acne scars, acne vulgaris, benign epidermal pigmented lesions, photodamage, and fine wrinkles resulting in an even and tight skin (Fischer et al. 2010).

Complications from chemical peels are uncommon when performed by an experienced dermatologist. They are more common in darker-skin patients and with medium and deep peels as compared to superficial peels. These complications may be prevented by proper patient selection, patient counseling, adequate priming, and with good intra-peel and post-peel care. Off-face site, especially the neck, can be more vulnerable for all these treatments, because these areas have thin skin and fewer pilosebaceous units and blood vessels (Landau 2008).

The Dermis

The dermis represents the inner layer of the skin localized between the epidermis and subcutaneous fat. It is a connective tissue composed of three main compartments: the cellular, being the fibroblasts the main cell type; the fibrillar, collagen and elastic fibers; and amorphous interstitial substance, a kind of gel rich in glycosaminoglycans in which the other compartments are embedded (Fig. 3).

The dermis lies on the subcutaneous tissue or hypodermis. The subcutaneous tissue is not considered part of the skin, being characterized as part of the soft tissue of the body. It consists of lobules of adipocyte limited by collagenous septa that contain the neurovascular bundles.

The dermis is divided into two portions, the papillary dermis and reticular dermis. An

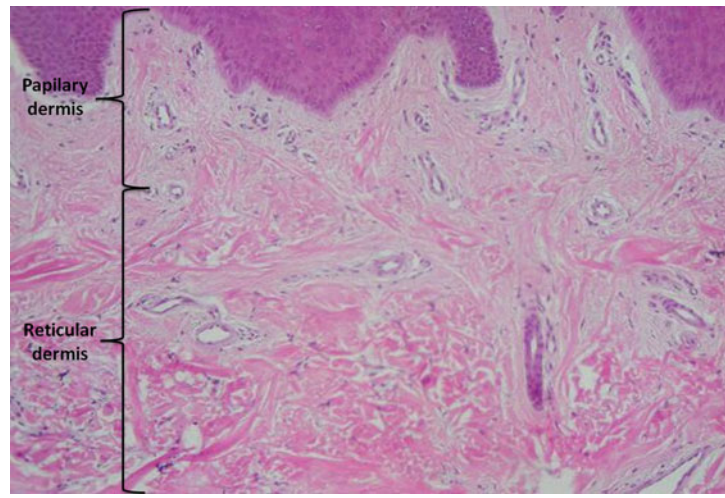

Fig. 3 Dermis. The dermis is a tissue with large amount of intercellular substance, so the fibroblasts are sparsely distributed and intermingled by large amount of collagen fibers and ground substance. Collagen fibers are eosinophilic (*pink*) and the ground substance is mostly removed during histologic process, giving rise to clear spaces between collagen fibers in sections of tissue (H&E, 100x)

imaginary line, parallel to the skin surface, that joins the vessels of the superficial vascular plexus limits these portions.

The papillary dermis is located more superficially. It has a relatively loose aspect because it is rich in amorphous interstitial substance and has more delicate, thinner, and less eosinophilic collagen bundles than those found in the reticular portion of the dermis. However, the papillary dermis has a higher density of fibroblasts than the reticular dermis. *Fibroblasts* are fusiform cells with oval nuclei that are immersed in the extracellular matrix of the dermis. The loose aspect of the papillary dermis facilitates the diffusion of oxygen and nutrients, which come out of the capillary vessels and reach the epidermis.

The reticular dermis contains thicker and more eosinophilic collagen bundles separated by interstitial amorphous substance. The collagen bundles of the reticular dermis are disposed in several directions and in different planes disposed in parallel to the skin surface. In this way, some bundles are seen in longitudinal sections, while others are sectioned transversally.

As the epidermis, the dermis thickness also varies according to the anatomical location, measuring from 0.3 mm on the eyelids to 3.0 mm or more on the back.

Collagen fibers are the supporting framework of the integument and are associated with skin stretch limitation. On the other hand, the elastic fibers are responsible for the skin quick return to its original position when the tensioned skin is released. The elastic fibers are not seen in routine sections stained with hematoxylin and eosine, requiring special stains like orcein or Verhoeff-Van Gieson.

Unaesthetic Conditions Involving the Dermis

Present at sun-exposed skin, solar elastosis is a product of a chronically sun-exposed fibroblast, resulting in a damaged cell that produces altered collagen fibers abnormally basophilic. It is an acellular basophilic material with a fibrillar appearance, deposited in the dermis of body areas chronically irradiated by the sunlight. The term elastosis derives from the property of this substance to stain by methods directed to elastic fibers (Ackerman 1997; Bolognia et al. n.d.; Calonje et al. 2011; Goldsmith et al. 2012; Lever and Elder 2005). The presence of elastosis is one important factor implied in the photoaging of the skin, contributing for phenotypic features of photoaging: mottled pigmentation, superficial wrinkles, dry and rough skin texture, loss of skin tone, and cutis rhomboidalis (thickened, deeply fissured skin seen on the back of the chronically sun-exposed neck).

Many cosmetic procedures aim to restore the amount of collagen lost during the aging process (neocollagenesis) or to push elastosis for deeper portion through promoting fibroplasia of the superficial dermis and making photoaging less noticeable. Such procedures include medium and deep peelings, microneedling, microfocused ultrasound, and ablative lasers. On the other hand, the fillers restore the volume missed by the decrease in amount of collagen and other components of the dermis. Initially, the main aim with dermal filler treatment was to correct lines and wrinkles. Therefore, a better understanding of the complex alterations associated to aging has provided an extending of our approach to volume replacement treatment, with emphasis on volume restoration in the midface. This approach requires deep knowledge of facial anatomy; the interactions of the skin, soft tissue, muscle, and bone; and about the beauty concept, which varies greatly with ethnicity and gender.

The physician should keep in mind that the potential exists for complications, especially in the hands of a novice injector. Fortunately, most complications are minor and transient in nature, although they might significantly affect patients physically and psychologically. Major complications are rare, but they can produce permanent, disfiguring damage. Complications are best prevented with careful planning. Knowledge of both facial anatomy and the specific properties of each filler are critical. In addition, managing patient expectations is an important element in the pretreatment preparation. Both arterial embolization and venous obstruction are extremely rare;

however, every office should be prepared for such an event.

It is interesting to explain the mechanism of action of microfocused ultrasound (MFU), which uses low levels of energy (0.4–1.2 J/mm^2 at a frequency of 4–10 MHz) to treat superficial layers of the skin. An MFU beam can pass harmlessly through the skin to target subcutaneous tissue at a focal point. This ultrasound energy causes cellular friction, raising the heat in the targeted area. This heat in turn acts on the fibroblasts that synthesize collagen. This device precisely heats the tissue containing fibroblasts to 60–70 °C, the point at which collagen fibrils break apart and contract in small (less than 1 mm) thermal coagulation points (TCPs) to a depth of up to 5 mm, while sparing adjacent tissues. Denaturing collagen fibers impairs their function, and the body responds through natural wound healing by creating new collagen (neocollagenesis). Two phases of tightening occur; an initial posttreatment phase takes place immediately due to the contraction and denaturation of collagen at the TCPs; a second stage of lifting then occurs as the body initiates an inflammatory response, stimulating the synthesis of new collagen with improved viscoelastic properties. Macrophages engulf and break down "injured" tissue and attract fibroblasts to promote repair. MFU is an effective and safe noninvasive form of treatment to lift and tighten skin, which gives patients a fresher, natural look with minimal discomfort and no downtime.

Epithelial Adnexa of the Skin

The dermis contains epithelial adnexa derived from the epidermis, namely, hair follicles, sebaceous glands, apocrine glands, and eccrine glands. The first three are related anatomically and embryologically, while the latter is completely independent from the others structures.

Hair follicles are present all over the body surface, with the exception of the palms and soles. Hair follicles undergo continuous cycles of growth (anagen), involution (catagen), and rest (telogen). The anagen is the productive stage, when the hair shaft is produced. Anagen phase lasts around 2–3 years, and, on the scalp, approximately 85% of the hair follicles are in this phase. The catagen is the stage in which the follicle involutes. It lasts 2–3 weeks and, on the scalp, it corresponds to the least amount of the hair follicles, around only 1%. The telogen is the resting stage of the follicle lasting 2–3 months and, on the scalp, around 14% of the hair follicles are in telogen.

The hair follicles are also classified according to their size. Terminal hair follicles produce hair shafts larger than 0.06 mm in diameter, and their bulb are located in the deep dermis or in the subcutis, while velus hair follicles produce hair shafts smaller than 0.03 mm in diameter, and their bulbs may be as superficial as the transition between the papillary and reticular dermis. Hair follicles with hair shafts between 0.03 and 0.06 mm in diameter are called intermediate follicles.

The upper part of the hair follicle does not change according to the stage of the cycle of the follicle and is divided in infundibulum and isthmus. The inferior portion of the hair follicle changes remarkably in each one of the stages.

The regeneration of the skin is by multiplication of the epidermal basal cells and/or from cells of the hair follicles, when the whole epidermis is destroyed. These cells migrate out of hair follicles in order to repair the damaged tissue (Fischer et al. 2010).

Sebaceous glands have a piriform lobules constituted mainly by mature sebocytes, i.e., epithelial cells with broad cytoplasm containing multiple lipid-rich vacuoles that look like empty on sections of tissue. Externally, the lobules display a single and inconspicuous layer of indistinct undifferentiated cells with scant cytoplasm. The sebaceous lobule is connected to a duct that ends in the hair follicle at the level of the transition between the infundibulum and the isthmus.

The secretory portion of the apocrine glands is coiled, located at the deep dermis or subcutaneous fat, and composed by two layers of cells. The external layer is composed by flattened myoepithelial cells, while the inner layer is composed by cuboidal or columnar cells with decapitation secretion. The secretion flows throw the

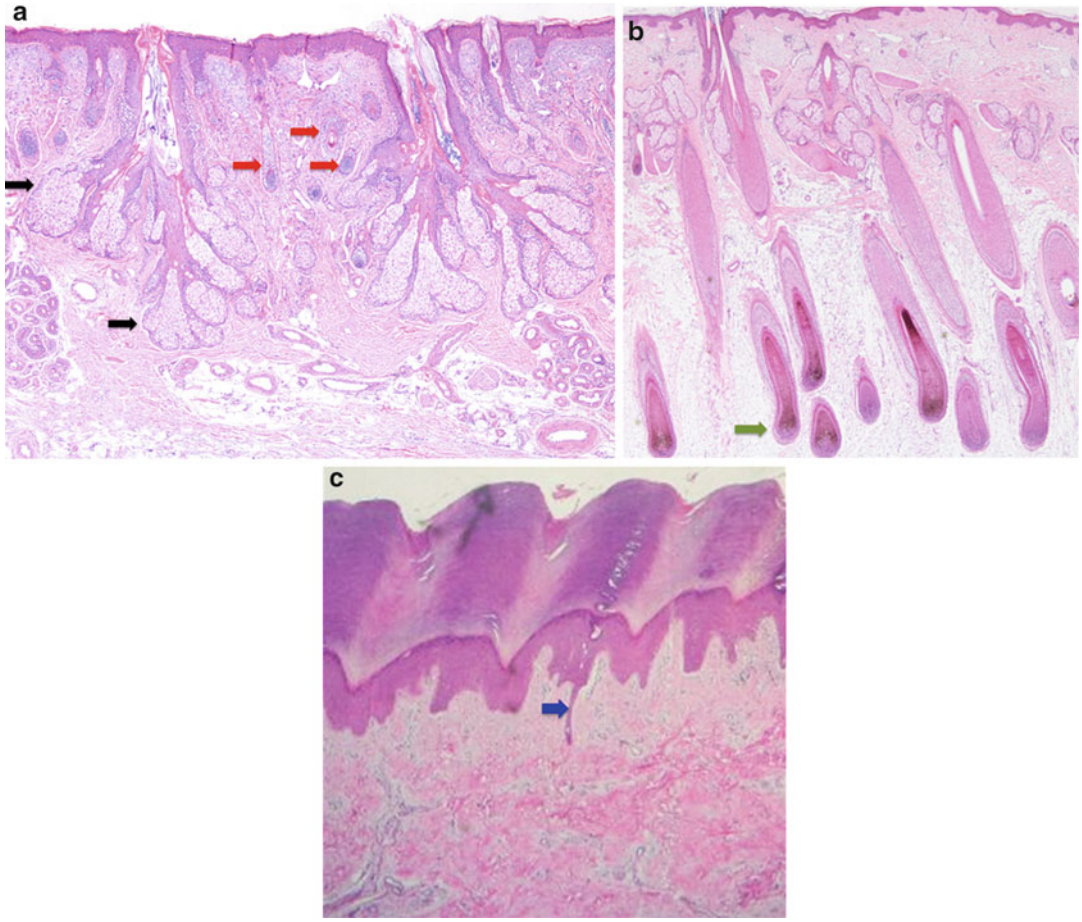

Fig. 4 Comparison between glabrous skin of the face, scalp skin, and volar skin. (**a**) Glabrous skin of the face (elderly patient). Note that sebaceous glands are prominent (*black arrows*) and the hair follicles (*red arrows*) are very small (vellus type). The bases of these follicles are situated in the superficial portion of the reticular dermis (H&E, 100x). (**b**) Scalp hair. The hair follicles are terminal ones, producing thick hair shafts. The inferior portion of the follicles reaches the hypodermis (H&E, 20x). (**c**) The volar skin, in the palms and soles, presents a thicker epidermis, with a compact stratum corneum. There are no hair follicles, although eccrine glands are frequent. In this photomicrograph, it is possible to see the insertion of an eccrine duct in the epidermis (*blue arrow*) (H&E, 100x)

apocrine duct that ends in the hair follicle at the level of the infundibulum.

The *eccrine glands* are not related anatomically and embryologically to the pilosebaceous-apocrine unit. It is composed by a secretory portion that is coiled and located in the deep dermis or in the subcutaneous fat, similarly to the apocrine gland, but, on the other hand, with smaller and more regularly shaped lumens. The secretory portion of the eccrine gland is also formed by two rows of cells, the external one being flattened myoepithelial cells and the inner one, cuboidal epithelial cells, without decapitation secretion. The eccrine duct has a straight portion that crosses the entire dermis and penetrates directly through the epidermis. The acrosyringium, the intraepidermal portion of the eccrine duct, is spiraled and functions as a path outside for the sweat produced to be discharged at the skin surface.

Histologically, the eccrine and apocrine ducts are identical. They are both composed by two rows of cells. The cells of the outer row are cuboidal with small round nuclei and scant cytoplasm (poroid cells), while the cells of the inner row have larger nuclei and ample eosinophilic cytoplasm (cuticular cells) (Fig. 4a–c).

The distribution and density of hair follicles over the body influence the regeneration potential of the skin. Since, the facial skin has a larger density of vellus hair and also a high proliferative activity associated with a good hydration, this topography has a rapid reepithelization after procedures. Recovery of the facial skin function, after any aggression to its integrity (chemical peels or laser therapy for example), is faster than off-face sites (Proksch et al. 2008; Boer et al. 2016).

The skin of most of the body has fine, almost inconspicuous hair, except for the palms and soles. Sebaceous glands are associated with hair follicles and are responsible for producing an oily secretion called sebum to the skin surface. Sebum, in conjunction with lipids from the corneal stratum and the perspiration produced by sweat glands, form a thin layer that lubricates the epidermis to protect from moisture loss, avoiding excessive water loss (Proksch et al. 2008; Boer et al. 2016).

Sebaceous glands are most concentrated on the face (especially on the T zone), scalp, neck, upper back, and interscapular area. They are largest on the forehead, nose, and upper part of the back. Thus, it is expected that these areas present high values of hydration, while lower values are observed on the forearms and mainly the shins (Ackerman 1997; Scheuplein and Blank 1971).

Therefore, the distribution and density of cutaneous appendages over the body influence the degree of hydration of the skin. With the exception of the palms, soles, and dorsa of the feet, sebaceous glands of various sizes are distributed over the entire skin surface.

These distinctive aspects of the skin hydration influence on its regenerative properties and, therefore, should be of medical knowledge prior to a cosmetic procedure.

However, the physician must be aware of the peculiarities of each individual by evaluating the degree of oiliness of the skin before performing invasive aesthetic procedures. The production of sebum is bigger in men than in women and it decreases with skin aging (Fore 2006). People with oilier facial skin, for example, require a more intense preparation for chemical peels then not-oily and thin-skinned people.

Vascularization of the Skin

There are two distinct blood vessel plexuses in the dermis: a superficial plexus that lies between the papillary and reticular dermis and deeper one, between the reticular dermis and the hypodermis. They are arranged parallelly to the skin surface and are interconnected through communicating vessels that cross the dermis vertically.

As previously said, the epidermis has no blood supply of its own. Dermal capillaries provide blood supply responsible for delivering nutrients and circulatory support to the epidermis.

Also the system of capillaries and venules in the dermis plays an essential role in the control of body temperature and blood pressure.

Innervation of the Skin

The skin is a sensory organ. It has an autonomic motor and a somatic sensory innervation. The motor innervation acts on eccrine and apocrine glands, blood vessels, and erector pili muscle.

The sensory innervation is involved in pain, itching, soft and discriminatory touch, pressure, vibration, proprioception, and the thermal sensation. It consists of free nerve endings and specialized corpuscles: Meissner's and Pacini's corpuscles.

The Meissner's corpuscles are sensory organelles specialized in sensitivity to light touch. They are present just beneath the epidermis, within the dermal papillae. Meissner corpuscles are present on many areas of the body but they are concentrated in areas where sensitive to light touch is important such as hands, feet, penis, and vulva.

The Pacinian corpuscles are another sensory organelle responsible for sensitivity to vibration and pressure. They are located deep in the dermis and they are morphologically similar to an onion

bulb (Ackerman 1997; Bolognia et al. n.d.; Calonje et al. 2011; Goldsmith et al. 2012; Lever and Elder 2005).

Muscles

The smooth muscles are the ones that have no voluntary contraction. It is innervated by the autonomic nervous system. In the skin, smooth muscle is present in the erector pili muscle, the dartos muscle (present in the scrotum, vulva, and nipples), and in the walls of arteries and veins. The erector pili muscle is inserted in the dermoepidermal junction on one side and on the hair follicle on the other side.

Striated muscles are those voluntarily controlled. In the skin, they are only found in the face. The face is the only anatomical site where striated muscles are inserted directly into the skin, being responsible for facial expressions (Ackerman 1997; Bolognia et al. n.d.; Calonje et al. 2011; Goldsmith et al. 2012; Lever and Elder 2005).

The repetitive contraction of the facial muscles over the years is responsible, along with other factors, for the development facial wrinkles, which in the beginning are dynamic lines, and later becomes fix and deeper. Botulinum toxin, a neuromodulator protein, blocks the release of acetylcholine at the neuromuscular junction, providing temporary weakness or paralysis of muscles responsible for the formation of the wrinkles (Fig. 5).

A precise knowledge and understanding of the functional anatomy of the mimetic muscles is absolutely necessary to correctly use botulinum toxins in clinical practice. As dermatologists, we also need to consider the anatomic differences between men and women and how we approach the use of neuromodulators.

Adverse effects are usually mild and transient. The most common substantive complication is excessive or unwanted weakness, which resolves as the effect of the toxin is lost gradually. Brow ptosis, eyelid ptosis, neck weakness, dysphagia, and diplopia may occur. Knowledge of the functional anatomy and experience with the procedure help injectors avoid complications. In the future, the development of new potent toxins with better effectiveness and longer duration of effect will further aid this expanding and interesting field of chemodenervation.

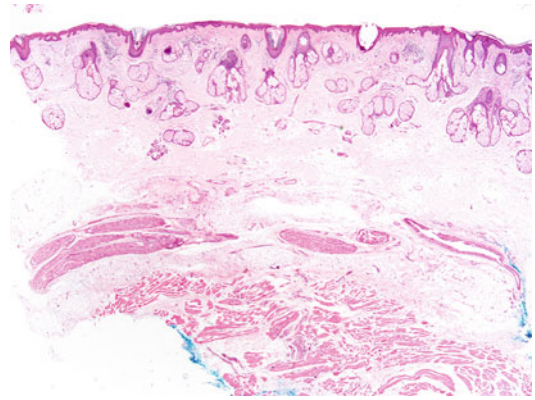

Fig. 5 Skin of the face. On the bottom of this tissue's section, striated muscle fascicles are found. These muscles are the targets of botulinum toxin effects (H&E, 20x)

In sum and in short, a firm understanding of normal skin structure and peculiarities of each different anatomical site is a requisite for a correct choice of the most adequate therapy for the patient complaint.

Take-Home Messages

- Facial skin has a high proliferative activity, a good hydration, and a larger density of vellus hair follicles, which allows it a rapid reepithelization and recovery of the skin barrier function after any aggression to its integrity, such as chemical peels or laser treatments, for example.
- The distribution and density of cutaneous appendages (hair follicles, sweat and sebaceous glands) over the body influence the degree of hydration of the skin.
- Sebum, in conjunction with lipids from the corneal stratum and the perspiration produced

by sweat glands, forms a thin layer that lubricates the epidermis to protect from moisture loss, avoiding excessive water loss.

- The regeneration of the skin is by multiplication of the epidermal cells and/or from cells of the hair follicles, when the whole epidermis is destroyed. These cells migrate out of hair follicles in order to repair the damaged tissue.
- Chemical peels provoke a wound in the skin and the regeneration process replaces part of the, or the entire, epidermis and induces also neocollagenesis resulting in an even and tight skin. Chemical peels help to improve photodamage, wrinkles, acne, scars, and pigmentary changes.
- Non-ablative treatments target the lower layers of skin (dermis) while leaving the skin's surface (epidermis) unharmed and intact. Ablative laser resurfacing targets both the surface and the lower layers of skin by injuring or "ablating" the surface of skin. The choice of ablative and non-ablative laser depends on downtime and expectations of your patient.
- A precise knowledge and understanding of the functional anatomy of the mimetic muscles are absolutely necessary to correctly use botulinum toxins in clinical practice; as dermatologists, we also need to consider the anatomic differences between men and women and how we approach the use of neuromodulators.
- The initial aim with dermal filler treatment was to correct lines and wrinkles, but an increased understanding of the complex changes that occur with aging has changed our approach to volume replacement.

Cross-References

- ▶ Approach in Photodamaged Skin, Melasma, Acne, and Rosacea
- ▶ Evaluation and Classification of Aging

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Part II

Daily Approach to Cosmetic Dermatology

Anamnesis and Physical Evaluation

Regina Casz Schechtman, Maria Luiza C. F. Santos Chiganer, and Angela Schwengber Gasparini

Abstract

Dermatology is a visual art; cutaneous signs have a significant role in dermatological diseases and also in cosmetic dermatology. The consultation in cosmetic dermatology is different from a consultation in any other medical specialty, but can be similar in many aspects. The relationship between the physician and the patient has always been and still is the successful key for coherent procedures without "overdoing" and leading to satisfaction on both sides. It is a must to go beyond prescribing interventions or treating unsightly conditions; we need to provide a good guidance on prevention and maintenance of skin health. A complete and well-directed anamnesis will be the greatest instrument for achieving this individual globally and the proper way to try to understand patient's expectations regarding the final outcome. It's important to remember that sociocultural relations should be maintained when thinking, proposing, indicating, and performing cosmetic dermatological treatments and aesthetic procedures.

Keywords

Cosmetic • Dermatology • Procedures • Anamnesis • Intervention

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Contents

Introduction

The term cosmetics is a neologism adopted from the English language – cosmetic dermatology – considering that the cosmetic word in Brazil is related to aesthetics, cosmetic's use, or beautician's activity. In fact it is an area of dermatology dedicated to study and intervene in "unaesthetic" dermatosis in which treatments are completely grounded on scientific basis.

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Dermatology is a visual art; cutaneous signs have a significant role in dermatological diseases and also in cosmetic dermatology. Careful observation of details and learning how and what to see beyond increase our medical assessment of patient's complaints, making us better doctors in the field of cosmetic dermatology. For dermatologists, especially the ones who deal with beauty, knowledge and the study of art should be of great value to improve patient's evaluation in clinical practice. It's important to remember that sociocultural relations should be maintained when thinking, proposing, indicating, and performing cosmetic dermatological treatments and aesthetic procedures that interfere with the lines of facial expression and the natural appearance of the cosmetic patient.

The Consultation

The dermatologist who chooses to work in this area must have a great deal of knowledge in general medicine and dermatology; in other words, consultation in cosmetic dermatology can be the first contact of the patient with this specialty; thus dermatologist's role in the anamnesis is to observe at physical examination the presence of suspicious skin lesions of cancer, advanced photoaging, as well as cutaneous manifestations of systemic diseases.

The consultation in cosmetic dermatology can be different from a consultation in any other medical specialty, but it is similar in many aspects. The relationship between the physician and the patient has always been and still is the successful key for coherent procedures without "overdoing" and leading to satisfaction on both sides. In cosmetic dermatology we must go beyond prescribing interventions or treating unsightly conditions; we need to provide a good guidance on prevention and maintenance of skin health, particularly in relation to cleansing, hydrating, and sun protection.

The most important pillar for building a successful relationship between physician and patient is the way the physician can value patient's complaints. Often a relatively insignificant complaint may be of great annoyance to the patient. Knowing how to value patient's complaints is an exercise that we should practice everyday. Since often what the patient verbalizes as a desire is only waiting for our sensitivity to capture what was not verbalized, it challenges us on how much we are prepared technically to help him or not.

It is already extensively known that there are two types of self-image: (1) the self-image we have within our subconscious and the image of how we interact with the outside world and (2) the other image we believe that others should have about us (Odo and Chichierchio 1998). So, these complaints that are frequently considered insignificant may represent the overflow of a low self-esteem, of social phobias, or even a distortion of the self-image. The physician at that time has a duty to be able to show to the patient what technically in fact makes the difference in his or her face and look out for worthy solutions to patient's complaints, thus enhancing their self-esteem through an objective and technically relevant analysis.

The fundamental item for the success of cosmetics interventions always will be a good clinical indication (Coimbra et al. 2014).

The Anamnesis

A complete and well-directed anamnesis will be the greatest instrument for achieving this individual globally and the proper way to try to understand patient's expectations regarding the final outcome.

It would be of major importance to know patient's previous diseases, always making notes of all drugs already used or in use, any allergies, previous surgeries, and family history, asking about other previous aesthetic treatments, and investigating about products used and whether it was temporary or a permanent product, as well as the degree of satisfaction for the patient. It is also important to learn about patient's lifestyle, outdoor works, sun habits, sunscreen use, inquiring about the ability to be absent from work or his daily routine, as well as to know about resources the patient can dispose on beauty treatments. One should be careful about the fears and anxieties of

major interventions. All these aspects must be thoroughly assessed before performing any minimally invasive procedure.

The Physical Examination

The patient's physical health also needs to be evaluated in this first contact prior to the possible proposed intervention (Monteiro 2010). Various procedures exclusively of aesthetic nature should be contraindicated in patients with bleeding and autoimmune disorders. It is extremely important to evaluate patients with a multidisciplinary approach, specially during some specific treatments like chemotherapy, for example.

The mental health assessment at the first consultation is a delicate matter and needs to be carefully accessed by the examining physician. It is extremely important to distinguish which procedures are well indicated to different individuals in the initial assessment of the cosmetic patient. The compulsion for aesthetic interventions is a frequent situation that dermatologists should deal with extreme caution. In fact, the physician cannot surrender to the eternal dissatisfaction of the patient, thus intervening in the aging process constantly and many times in an exaggerated and unnecessary way. Besides that, the cause of the real problem is not being accessed.

Patient Record

Recording all the information concerning the patient must be included in its medical report; this is the document with legal value for both patient and physician. It must include a detailed anamnesis, physical examination, laboratory test results, and all procedures performed. Apart from that it is wise to write down about the degree of patient's satisfaction. It is a must to take photographs and to register the name and the batch number of the products used, in addition to medical prescriptions performed at each visit, including post-procedure consultations. A well-written patient consent form is of legal support for the medical professional as well as a valuable information for the patient. It is necessary to describe everything that the patient was told about, all the possible side effects of the procedure to be performed, possible risks, and potential complications that can occur during the treatment as well as possible duration of each effect. Post-procedural care also needs to be included in the patient consent form to avoid complications. This term must be signed by the patient with two copies: one for the patient and another for the professional.

Photographic Documentation: Before and After

Dermatology is a visual art and cutaneous images have an important role in general and cosmetic dermatology. In this context, digital photography becomes an important tool in the clinical practice when dealing with cosmetic patients (Monteiro 2011).

A proper record is extremely important for both patients and physicians. The photograph should be considered far beyond its documentary nature. A well-executed photograph, technically perfect and visually refined, is able to reveal precious information from the patient. Therefore, the medical documentation must be technically perfect and accurate; important objects and their details must all be in focus and sharp. It must be standardized and reproducible, with a clear picture of what was seen, with professional quality. Only then it can be considered of legal value.

The correct and standardized lighting is essential in particular, when it comes to photos intended for comparisons of "before" and "after" some cosmetic intervention. There is no value in comparing photos taken with different incidences of light or varying degrees of exposure.

It is by using this apparatus that the doctor and the patient can compare the area treated before and after the cosmetic procedure was performed. It is advisable that patient be informed by the doctor of individual characteristics that go unnoticed, so that they would not

become an issue after the procedure was already performed.

The photographic material must always maintain the same standard in order to be used as a comparison: the distance between the patient and the camera has to be the same as well as the background; same angles and lighting must be maintained (Miot et al. 2006). It is recommended whenever possible to use the same equipment for all photographs taken for comparison purposes. Therefore, the offices designed for cosmetic dermatology should always include a special space or room, whenever possible, intended for this purpose.

What and When to Photograph

We should always remember to photograph our patients, for interventions with expected specific results, aesthetic frequent procedures, all treatments with possible complications such as scars, uncover potentially malignant lesions, and difficult cases, and also remember to photograph patients with potentially dangerous psychological profile or unstable. Those patients could have a nonrealistic expectation.

Patient's Expectation Versus Possible Results

The patient who seeks the physician to perform cosmetic procedures demands an objective positive result from the cosmetic intervention that is exposed previously during the first consultation. In order to achieve the patient's expectations regarding the cosmetic treatment and the possible outcome, it is necessary that the signs of facial aging have been thoroughly explained by the physician and fully understood by the patient. So we have to be sure that the patient understands the possible outcome we can provide and contemplate a more harmonious result individually. Undoubtedly the greatest tool we have against the frustrations of our cosmetic patients is the full and complete understanding of the dimensions and geometry of the face. We must have in mind that it is important to treat our patients globally, for them to see as themselves being more beautiful and younger after the intervention. Even without taking into account the financial aspect, a frustrated expectation from the patient would also be a frustration to its physician.

The Aging Process

Nowadays there is a world trend to consider the contour of the face as being the most important part for the aging process. The main idea is that, treating the face contour, the patient has the impression to have a more youthful and well-cared face. There are specific characteristics of the aging process that are unchangeable; thus we can manage with minimally invasive procedures to improve the geometry of the face but not to prevent the progression of the aging process. The great responsible for our aging is not the gravity but the absorption of our fat compartments, we shrivel up, and so the main face ends up with a "melted appearance" (Coimbra et al. 2014).

There are four main pillars of the cosmetic treatment that cosmetic dermatology can act in order to treat the aging process:

1. Skin treatment
2. Treatment of the muscles
3. Procedures to give bone support
4. Restoration of fat compartments

The main point that patient must understand when seeking for treatment for the aging process is that we cannot stop the natural evolution but we can treat and prevent this continuous process.

A good distinction between the light and the shadow zones of the face is the key for the best technique we can apply to mislead the aging process (Coleman and Grover 2006). All the concave structures provide a shadow zone in the aging face. So we look for interventions to let the face of the woman convex from the upper third to the lower third of the face. Yet in men, it is recommended to keep the straight lines and thus provide more aesthetically proportional faces to comply male beauty standards.

When we will propose a cosmetic intervention in the face of the patient, it is important to divide

the face into three thirds: the forehead being the upper third, malar and zygomatic regions being the middle third, and chin and jaw regions being the lower third. The first action to be taken place is the intervention to give bone support and improve sustentation and laxity of the face, before thinking to erase any superficial groove.

With the advent of the idea of volumizing, nowadays interventions can last longer than in the past. The modern hyaluronic acids are designed to act exactly in restructuring face sustentation. They are lasting for longer periods of time, thus providing more aesthetically relevant and satisfactory results than just the old ones which were designed to fill the visible grooves without treating the cause of the aging appearance of the face.

Conclusion

In this special area within the dermatology, the cosmetics, our eyes cannot merely have a technical look. Our perception should not only be guided by science, though we must also have the ability of an artistic look (Shapiro and Rucker 2003). In addition to the scientific expertise, the physician must have the ability to artistically evaluate the patient and to evaluate which of those wrinkles belongs to patient's self-image and what in fact can be treated without erasing the mirror of the emotions that the skin reflects.

Take-Home Messages

- A complete and well-directed anamnesis is the best instrument to achieve all the information necessary to understand the patient globally.
- Careful observation of details and learning how and what to see beyond increase our medical assessment of patient's complaints and expectations.
- It would be of major importance to know patient's previous history (drugs used, any allergies, previous surgeries, family history, previous aesthetic treatment, degree of satisfaction).
- It is important to learn about patient's lifestyle: outdoor works, sun habits, sunscreen use, and ability to be absent from work and daily routine.
- Dermatologists should know patient's fears and anxieties about common interventions in cosmetic dermatology before performing any minimally invasive procedure.
- Photography is an important tool in the clinical practice when dealing with cosmetic patients. A proper documentation of before and after procedures is extremely important for both patients and physicians.

Cross-References

- ▶ Approach in Photodamaged Skin, Melasma, Acne, and Rosacea
- ▶ Chemical Peelings: Face
- ▶ Evaluation and Classification of Aging
- ▶ Lasers, Lights, and Related Technologies in Cosmetic Dermatology
- ▶ Photoprotection: Concept, Classification, and Mechanism of Action
- ▶ Psychological Approach in Cosmetic Dermatology
- ▶ Skin Anatomy, Histology, and Physiology

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Psychological Approach in Cosmetic Dermatology

David Ernesto Castillo, Katlein França, and Torello Lotti

Abstract

Cosmetic psychodermatology is a new science that studies the psychological aspects of cosmetic patients. The complex relationship between mind and skin is the focus of study of psychodermatology and must be understood by cosmetic dermatologists. The patient's mental status, expectations, background, and the possible presence of psychiatric comorbidities should be recognized and addressed prior to cosmetic procedures to obtain the best results. Cosmetic dermatologists must be trained to evaluate the psychological aspects of their patients. This chapter provides concepts of psychodermatology and its association to cosmetic dermatology, the common psychiatric disorders that can be seen in dermatology and advices to establish a good doctor-patient relationship.

Keywords

Cosmetic psychodermatology • Psychodermatology • Cosmetic procedures • Dermatologic procedures • Psychiatric disorders • Doctor-patient relationship • Patient's expectations • Difficult patients • Referring patients

Contents

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Introduction

Psychodermatology is an integrative science that studies the interaction between skin and mind. The study of this complex cycle, in which mind and skin are linked and influencing each other, has expanded in the recent decades (França et al. 2013). This increasing interest, the recent advances in psychodermatology and the economic growth and, thereby growing interest in cosmetic procedures have led to the creation of a new science called "cosmetic psychodermatology." According to França, this new science was created to understand the psychological aspects, emotions, and expectations of patients seeking cosmetic procedures (França 2016).

Epidemiological studies have shown that many patients with psychiatric conditions never receive appropriate treatment (Narrow et al. 1993; Kessler et al. 1999; Zimmerman et al. 2005). Thereby, in modern medicine, cosmetic psychodermatologists must be trained to deal with the psychological aspects of their patients. This involves learning skills to conduct a basic psychological evaluation to know the patient's expectations, recent experience with procedures and outcomes, as well as the creation of an appropriate doctor-patient relationship, as the keystone for a good doctor-patient interaction (Goold and Lipkin 1999; França et al. 2015).

This chapter will discuss the concept of cosmetic psychodermatology and its application in modern medicine, the psychological aspects of dermatologic patients, including the most common psychiatric disorders, the patient's expectation, how to deal with the difficult patient, and the importance of a good doctor-patient relationship.

Worldwide the demand for cosmetic procedures has expanded in the last decades (Sacchidanand and Bhat 2012). More and more patients are seeking esthetic procedures every year. In consequence, cosmetic dermatologists must develop skills to understand this diverse population. Even though adult females still account for the majority of patients seeking cosmetic therapy, dermatologists should be prepared to deal with patients of any sex or age as the interest for cosmetic procedures among young patients and males is increasing rapidly (França 2016). The increasing interest combined with an improved affordability and income of the population has driven the awareness for cosmetic procedures. There are several reason that may lead a patient to seek cosmetic procedures, and these include personal desire (embarrassment, vanity), society influence, and also psychiatric and psychodermatological disorders (Šitum and Buljan 2010; Sacchidanand and Bhat 2012).

Dermatologists that will perform a cosmetic procedure must consider the magnitude of the psychological aspect of the patient. There is a well-established relationship between mind and skin that must be taken into account (França 2016). Physicians should perform a psychological evaluation prior to the cosmetic procedure to identify those patients that will not benefit from the procedure. A thorough evaluation to explore the patient's mental status, false expectations, doubts, and previous experiences will help the physician to recognize psychiatric disorders that will interfere with the procedure and that might worsen the patient's condition. Thereby, basic knowledge about common psychodermatological disorders such as obsessive-compulsive disorders and body dysmorphic disorder is very useful for all physicians (Jafferany 2007). The dermatologist must provide clear information about possible outcomes and complications of esthetic procedures to avoid false expectations. This will increase satisfaction and prevent medicolegal complications.

Cosmetic Psychodermatology: A New Science

The scientific community has set a lot of interest on the interaction between mind and skin in the last decades. Psychodermatology was created to address the overwhelming evidence of the relationship between psychiatric conditions and dermatologic disorders. Physicians have placed special interest in developing this field of medicine combining concepts of dermatology and psychiatry (Koo 1995; França et al. 2013). Psychiatry focuses in the internal factors (psychic), while

dermatology focuses in the external factors (the skin) (Jafferany 2007; Rodríguez et al. 2011; França et al. 2013). The complex interaction between mind and skin comes from their ectodermal origin and helps to explain the high incidence rates (30–60%) of psychiatric disorders among these patients (Basavaraj et al. 2010).

In the last two decades, great scientific effort has been done to expand our knowledge about psychodermatology (França 2016). Recent advances in treatment combined with the increasing interest of patients in cosmetic treatment have driven concern about psychiatric disorder and its effects in dermatologic patients. More scientific information is being published every year about this specialty, increasing awareness among physicians (Jafferany and França 2016). Aspects such as mental evaluation, psychotherapy, and pharmacotherapy are of special interest, and close work between dermatologists and psychiatrists has been useful in the treatment of psychocutaneous disorders (Basavaraj et al. 2010).

The growing interest for cosmetic procedures and the new advances in psychodermatology have led to the development of a field named cosmetic psychodermatology (Sacchidanand and Bhat 2012; França 2016). According to França, this new subspecialty of psychodermatology originated from the combination of cosmetic dermatology and psychodermatology. Cosmetic psychodermatology involves the study of the social and psychological features of patients, their cultural background, expectations and experiences with previous cosmetic procedures, and the effects that these procedures produce on their lives (França 2016). In modern medicine, cosmetic dermatologists must be trained to provide a basic psychological evaluation and recognize psychiatric conditions in patients seeking cosmetic procedures (Scheme 1).

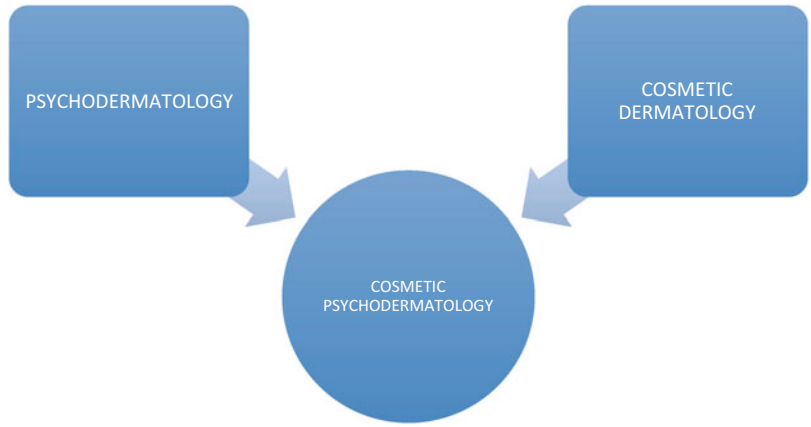
Knowing the Patient

Cosmetic dermatologists must know how important is to individualizing care for patients seeking esthetic procedures. These groups of patients are particularly seeking highest results. Thus, a good dermatologist must consider each patient's background and personality, emphasizing the patient's expectations, doubts, preferences, and goals to optimize care. Each patient must be treated with empathy and confidence in order to create a good doctor-patient relationship (França 2016). A pleasant conversation and a good relationship will allow an appropriate environment to gather the information needed to make a complete medical history. Personal, familiar, and psychological history must be collected carefully as many factors play a role on how the patient will respond to the procedure.

A dermatologist should have the ability to conduct a basic psychological evaluation. This evaluation will give an overview of the patient's mental status and will allow the physician to resolve the patient's doubts and fears about the procedure. Expectations, either real or false, negatively affect the outcomes of the procedure and need to be addressed immediately (Bowling et al. 2012). This is done by thoroughly evaluating the patient's concerns, beliefs, cultural backgrounds, and experiences with previous procedures during the interview (Jhon 1992; Bowling et al. 2012). If false expectations are present, the dermatologist must clearly explain why they are unrealistic and provide accurate information about the procedure, real outcomes, and complications (França et al. 2014). Finally, doctors must remember the importance of the doctor-patient relationship spending enough time to ensure the patent's welfare and understanding.

Common Psychiatric Disorders in Dermatology

Psychiatric disorders are relatively common disorders that can affect people of any age, culture, and income levels (França et al. 2014). They are defined as clinically significant behaviors or psychological patterns that cause distress and impair normal functioning (Stein et al. 2010; França et al. 2014).



Scheme 1 Cosmetic psychodermatology: New science that studies the relationship between cosmetic dermatology and psychodermatology. Created to understand the psychological aspects of patients seeking cosmetic procedures and how it can affect the patient's life. Information taken from (França 2016)

Among the common psychiatric disorders found in the dermatologic practice, there is body dysmorphic disorder (Conrado 2009). Dermatologists should be trained to recognized this disorder prior to cosmetic procedures and promptly refer the patient for expert evaluation. Other common psychiatric conditions seen in practice are obsessive-compulsive disorder, anxiety, personality disorders, and eating disorders (Jafferany 2007). All of them will disrupt the patient's overview about the procedure, and thus, these patients must be treated by a multidisciplinary group involving the dermatologist, psychiatrist, and psychodermatologist.

Body Dysmorphic Disorder

Body dysmorphic disorder is a chronic mental disorder frequently seen in cosmetic practice. It is characterized by excessive preoccupation with nonexistent or minimal defects in physical appearance (Bjornsson et al. 2010; Phillips 2004). These physical abnormalities are not perceived by others, and although it can focused on the whole body, it is more frequently focused on one specific part of it (Phillips 2004). The severity of the disorder varies among patients, ranging from a mild disease that might not interfere with daily activities to a severe condition that threatens life and can lead to suicide. Patients with body dysmorphic disorder see themselves as deformed and non-attractive, showing a marked discrepancy with their actual body appearance (Veale et al. 2003). These intrusive thoughts become obsessions which worsen when the patient's feelings are under evaluation and become difficult to control (Conrado 2009).

In order to cope and dissimulate these obsessions, patients with body dysmorphic disorder resort to time-consuming compulsions (Crerand et al. 2006). These patients engage in behavioral acts such as excessive mirror gazing, grooming, applying makeup, and cloth changing, and they seek multiple dermatologic and cosmetic treatments (Conrado 2009; Jafferany and França 2015). Others engage on mental compulsions such as comparing one's appearance with others (Jafferany et al. 2015). These behaviors are thought to reduce distress and impairment.

The estimated prevalence for body dysmorphic disorder in the general population is 1–2%, and there is no gender difference (American Psychiatric Association 2000; Crerand et al. 2006; Conrado 2009). Even though body dysmorphic disorder first manifest during adolescence, it is often diagnosed later in life when patients seek cosmetic treatment (Veale 2004). These patients more often complains of their nose (size, shape), skin (excoriation, acne), and hair (baldness, excessive body hair) (Conrado 2009). The last two are of great importance because they are associated with pathologic behaviors such as skin picking and hair plucking (Phillips and

Taub 1995). The dermatologist must know the difference between hair plucking in patients with body dysmorphic disorder and trichotillomania. While in body dysmorphic disorder hair plucking follows a specific reason (better appearance), in trichotillomania it does not (Conrado 2009). Body dysmorphic disorder is associated with higher rates of depression, anxiety, substance abuse, and personality disorders compare to other psychiatric conditions (Phillips et al. 2004; Crerand et al. 2006).

Among physicians, dermatologists are more likely to encounter patients with body dysmorphic disorder. The rate of this pathology for patients seeking dermatologic and cosmetic procedures ranges from 2.9% to 16% (Castle et al. 2004; Bellino et al. 2006; Vulink et al. 2006; Bowe et al. 2007; Taillon et al. 2013). Accordingly, the dermatologist must know how to recognize the disease to avoid cosmetic procedures in these patients, which will only worsen the psychiatric condition. It is also essential for the dermatologist to work closely with psychiatrists and psychodermatologists to provide prompt referral, prevent relapses, and achieve full compliance. Pharmacotherapy with selective serotonin reuptake inhibitors and cognitive behavioral therapy is the best approach (Phillips 2002; Crerand et al. 2006; Conrado 2009). The last one involves the use of behavioral exercises, cognitive techniques, and exposure therapy, which help to diminish the abnormal behavior and help the patient to integrate into society (Neziroglu and Khemlani-Patel 2002; Prazeres et al. 2013). Thereby, a good doctor-patient relationship based on trust and confidence is essential for appropriate management and to prevent multiple dermatologic visits and physician burnout.

Body dysmorphic disorder is classified in the spectrum of obsessive-compulsive spectrum disorders. To make the diagnosis, preoccupations cannot focus on noticeable defects or normal, non-pathological, appearance concerns (American Psychiatric Association 2013). The diagnostic criteria for body dysmorphic disorder from the 5th edition of the *Diagnostic and Statistical Manual of Mental Disorder* from the American Psychiatrist Association are listed below:

- Preoccupation with imaginary defects: Patient's concerns are not real or minimal and are not perceived by others. These preoccupations cannot be focused on real defects.
- Engaging on repetitive behaviors: At some point of the disease, the patient engages on repetitive, compulsive behaviors in response to the physical defect. Patients can perform real on mental compulsions. Examples: excessive mirror gazing, grooming, and hair plucking.
- Clinically significant: The preoccupation must cause clinically significant distress in social or occupational functioning.
- Rule out eating disorder: If patient's concerns are focused on body fat or weight and his/her symptoms meet diagnostic criteria for eating disorder, the eating disorder is the diagnosis and not body dysmorphic disorder.
- Must specify if:
  (i) Muscle dysmorphia: the patient's concerns are focused on having too small or insufficient muscle mass. This is true even if the patient is preoccupied with other body areas. This is associated with worse prognosis.
  (ii) Insight: Indicate the degree of insight regarding body dysmorphic disorder. This tells the doctor how convinced is the patient that his/her concerns are true. The patient may say, "I am ugly, I look deformed."

Major Depressive Disorder

Major depressive disorder (MDD) is a common and recurrent mental disorder characterized by episodes of depressed mood and lack of interest associated with impaired neurovegetative functions (appetite, sleeping), cognition (guilt, feeling of worthlessness), psychomotor retardation or agitation, and suicidal thoughts (Fava and Kendler 2000). These episodes cause clinically significant distress in social and occupational

functioning, and are not always precipitated by an external cause (Belmaker and Agam 2008). To make an appropriate diagnosis of major depressive disorder, the episodes of sadness cannot account for bereavement or be caused by the physiological effect of a substance or medical illness. Furthermore, physicians most recognized that patients with MDD might have signs and symptoms of mania, hence, meaning a diagnosis of bipolar disorder which implies a different diagnostic and treatment approach (Belmaker and Agam 2008).

The estimated lifetime prevalence of major depressive disorder in America is 16.2% (Kessler et al. 2003). Moreover, the prevalence of depression in dermatologic patients is as high as 30%, particularly for those with severe skin disorders such as psoriasis and rosacea (Filaković et al. 2008). Thereby, dermatologists must be prepared to face and diagnose this common and complex disorder. MDD usually begins during adolescence and adulthood life and most of these patients will have more than one episodes of MDD throughout their life, especially if the diagnose is made at young ages (Kessler et al. 2003; Kessler and Wang 2008). Several risk factors are identified for major depressive disorder, including gender (women), loss of interpersonal relationships, job loss, health problems, marital difficulties, history of sexual abuse (early in life), and poor parent-child relationship, among others (Kessler 1997; Fava and Kendler 2000). This is a highly comorbid disorder strongly associated with other psychiatric illness, being the most commonly identified anxiety disorders, substance abuse, and impulse control disorders (Kessler et al. 2003).

The treatment of major depressive disorder in dermatologic patients is complex and requires the conformation of a team involving the psychodermatologist and a psychiatrist in order to cover the aspects of both the mental and the somatic illness (Filaković et al. 2009). The pharmacotherapy of these patients should be based in the recent understanding of the role of the immune system by the release of pro-inflammatory cytokines and other immunomodulatory molecules in the development of both disorders (Katsambas and Stratigos 2001; Himmerich et al. 2006; Filaković et al. 2009). It is known that certain drugs such as selective serotonin reuptake inhibitors, that have proven to be very effective, have anti-inflammatory effects that help to improve the depressed mood and the skin disease, particularly if the skin disorder is related to an immune system alteration (Keshavan 1997; Szelényi and Selmeczy 2002; Filaković et al. 2009). Concomitantly, the psychotherapeutic approach must focus on interpersonal psychotherapy and cognitive behavioral therapy, which are as effective as pharmacotherapy for major depression disorder (Fava and Kendler 2000; Hollon and Dimidjian 2009). Other treatment therapies include atypical antidepressants (bupropion, mirtazapine, nefazodone, and trazodone), serotonin-norepinephrine reuptake inhibitors (venlafaxine), selective norepinephrine reuptake inhibitors (reboxetine), and electroconvulsive therapy (Fava and Kendler 2000).

The diagnostic criteria for major depressive disorder from the 5th edition of the *Diagnostic and Statistical Manual of Mental Disorder* from the American Psychiatry Association are listed below:

(A) Five or more of the following symptoms have been present during the same 2 week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.
   1. Depressed mood most of the day, nearly every day. This might be an irritable mood for children and adolescents.
   2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day.
   3. Considerable weight loss or weight gain (e.g., 5% or more change of weight in a month). Can also be a significant increase or decrease in appetite. For children, no gain of the expect amount of weight.
   4. Insomnia (difficulty falling or staying asleep) or hypersomnia (sleeping more than usual).
   5. Psychomotor agitation or retardation. Observed by others.

6. Fatigue or loss of energy nearly every day.
7. Feeling of worthlessness or extreme guilty nearly every day (not about being ill).
8. Decreased ability to think or concentrate nearly every day.
9. Frequent thoughts of deaths or suicide (not just fear of dying) or attempt to suicide or specific plan for committing suicide.

(B) These symptoms do not meet criteria for a mixed episode.

(C) The symptoms cause clinically significant distress in social, occupational, or other areas of functioning.

(D) The symptoms are not attributed to the physiological effects of a substance or medical condition.

(E) The symptoms are not due to grief or bereavement after the death of a loved one and persist for more than 2 months or cause significant functional impairment, excessive preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation.

Anxiety Disorders

Anxiety disorders are by far the most common psychiatric disorder (Kessler et al. 2005). These disorders are characterized by excessive worry that begin early in life and persist throughout it causing significant developmental, psychological, and functional impairment (Stein et al. 2014). Anxiety is a normal response to danger and is considered a very useful tool to deal with everyday life experiences (Staner 2003). However, when this response becomes pervasive, interfering with quality of life, cognitive and social functioning is considered pathologic (França et al. 2014). These common disorders are usually associated with other psychiatric and somatic disorders such as mood disorders and diabetes, creating a great burden for the patient and the society (Hettema et al. 2001; Koen and Stein 2011). Table 1 provides a list of the anxiety disorders, obsessive-compulsive related disorders, and trauma- and stressor-related disorders. It is important to highlight that in the 5th edition of the *Diagnostic and Statistical Manual of Mental Disorder* from the American Psychiatry Association, the obsessive-compulsive and trauma- and stressor-related disorders were removed from the section of anxiety disorders and are now classified separately.

Table 1 List of anxiety disorders, obesessive-compulsive related disorders, and trauma- and stressor-relatd disorders. Information taken from (American Psychiatric Association 2013)

Anxiety disorders	Separation anxiety
	Selective mutism
	Specific phobia
	Social anxiety disorder (social phobia)
	Panic disorder
	Panic attack
	Agoraphobia
	Generalized anxiety disorder
	Substance-/medication-induced anxiety disorder
	Anxiety disorder due to another medical condition
	Unspecified anxiety disorder
Obsessive-compulsive and related disorders	Obsessive-compulsive disorder
	Body dysmorphic disorder
	Hoarding disorder
	Trichotillomania (hair-pulling disorder)
	Excoriation disorder (skin picking)
	Substance-/medication-induced obsessive-compulsive and related disorder
	Obsessive-compulsive and related disorder due to another medical condition
	Other specified obsessive-compulsive and related disorder
	Unspecified obsessive-compulsive and related disorder
Trauma- and stressor-related disorders	Reactive attachment disorder
	Disinhibited social engagement disorder
	Posttraumatic stress disorder
	Acute stress disorder
	Adjustment disorder
	Other specified trauma- and stressor-related disorder
	Unspecified trauma- and stressor-related disorder

As any psychiatric condition, anxiety disorders must be treated by physicians with expertise in these pathologies. The dermatologists must recognize these common disorders and promptly refer the patient for expert evaluation by a psychiatrist. A combination of psychotherapy, cognitive behavioral therapy, and pharmacotherapy with selective serotonin reuptake inhibitors is the most effective therapy for all anxiety disorders and anxiety-related disorders (Koen and Stein 2011; Stein et al. 2014).

Personality Disorders

Personality disorders are enduring patterns of experiences and behaviors deviated from the expectations of society (Livesley et al. 2001). These are maladaptive, inflexible, and pervasive patterns that cause significant distress and persist over time, and must be differentiated from personality traits that are repetitive patterns on how people perceive and think about oneself and the environment (Livesley et al. 2001). The severity of the disease ranges from a mild disease to a severe condition that causes functional impairment in all areas of life. Personality disorders are divided in three clusters, A, B, and C. A single individual may show one or many patterns of personalities (Zimmerman et al. 2005). A brief explanation of the most important personality disorders is provided in Table 2.

The estimated prevalence of personality disorders in general population is 9–14.9% (Angstman and Rasmussen 2011). The most common personality disorders are avoidant, borderline, and obsessive-compulsive personality disorder (Zimmerman et al. 2005). There are some differences between genders. Dependant, passive-aggressive, and histrionic personality disorders are more common in females, rather obsessive-compulsive, schizotypal and antisocial personality disorders are more common in males (Maier et al. 1995; Zimmerman et al. 2001). Also, these disorders tend to appear at young ages and decline with time. Personality disorders are associated with substance abuse, anxiety disorders, sexual disorders, mood disorders, obsessive-compulsive disorder, and eating disorders (Angstman and Rasmussen 2011).

Many epidemiological studies have shown that most patients do not receive treatment for psychiatric conditions (Narrow et al. 1993; Kessler et al. 1999; Zimmerman et al. 2005). The mainstay of the treatment is individual and group psychotherapy, which is specific for each type of personality disorder (Angstman and Rasmussen 2011). Pharmacotherapy with antidepressants or antipsychotic drugs is reserved for patients with coexisting comorbidities (Angstman and Rasmussen 2011). Because suicidal ideations and attempts are common, extensive communication between the dermatologist and psychodermatologist is needed to create a safe environment and prevent negative outcomes.

The Patient and the Physician

Doctor-Patient Relationship

The doctor-patient relationship remains the keystone of medical practice (França et al. 2014). This interaction is the major medium by which the medical interview gathers information, diagnosis are made, compliance with treatment and care is accomplished, and must be guided by the bioethical principles of autonomy, justice, beneficence, and non-maleficence (França 2012; França et al. 2015). Susan et al. see the doctor- patient relationship as the major influence on practitioner and patient satisfaction, thereby contributing to practice maintenance, prevention of practitioner burnout and turnover, and it is the major determinant of compliance (Goold and Lipkin 1999).

The physician should begin the patient interview by greeting the patient, introducing himself, and using an open-ended question. The doctor must show empathy, respect, courtesy, and trust considered as “core conditions” to sustain an effective communication (França 2012). Furthermore, self-evaluation to enchase their communication skills, knowledge, and focusing on each patient as individual and unique is essential for an adequate doctor-patient relationship (Goold and Lipkin 1999). Following the initial approach,

Table 2 Brief summary of personality disorders. Information taken from (Livesley et al. 2001; Angstman and Rasmussen 2011; American Psychiatric Association 2013)

Cluster and type	Important clinical features
Cluster A (odd, bizarre)	Associated with schizophrenia
Paranoid personality disorder	Pattern of pervasive distrust and suspiciousness. They are isolated from others as they negatively interpret people's intentions and words and are constantly seeking clues to support these suspiciousnesses. Very sensitive to criticism. The most common defense mechanism is projection
Schizoid personality disorder	These patients do not desire or enjoy any form of social interaction and prefer engaging in solitary activities. Lack of close friends and show no interest in sexual relationships. Characterized by emotional coldness, flattened affect, and detachment from people including the family setting
Schizotypal personality disorder	Eccentric appearance, speech, beliefs, and magical thinking. These patients do not desire social interaction and many develop social anxiety. Interpersonal awkwardness and ideas of references are common. May present brief psychotic episodes
Cluster B (dramatic, emotional)	Associated with mood disorders and substance abuse
Antisocial personality disorder	Disregards and constant violation of social rules. These are very impulsive patients that lack guilt and pay no attention to the feeling of others. Very likely to commit crimes and to being in prisons. More common in male than females
Borderline personality disorder	Pattern of emotional instability and unstable interpersonal relationship. These patients are impulsive and have outburst of inappropriate anger. Feeling of emptiness and boredom. Engage self-mutilation and suicidal behaviors. More common in female than males. The major defense mechanism is splitting
Histrionic personality disorder	These are extremely dramatic persons that are constantly seeking attention and approval of others. They are overly concerned about their appearance and behave in a seductive and sexual manner. Relationships are usually superficial and lack honesty causing rejection of others. Thus, impairing social interaction as they are extremely sensitive to rejection and criticism
Narcissistic personality disorder	Characterized by grandiosity, self-entitlement, and arrogance. They need admiration and tend to demand special treatment. These patients lack empathy and usually exploit others. They feel underestimated and react bad to criticism with outburst of rage. People tend to see them as selfish, insensitive, and controlling
Cluster C (anxious, fearful)	Associated with anxiety disorders
Avoidant personality disorder	These patients are socially inhibited, see themselves as inept or inferior and are excessively concern about rejection and criticism. Feeling of inadequacy. Unlike schizoid PD they desire social interaction but will only establish a relationship if they are certain of being liked
Obsessive-compulsive personality disorder	Pattern of preoccupation with order, details, rules, organization, and schedules. Extremely perfectionist, which engage them in time-consuming behavior to increase productivity that limits social interaction. These persons are rigid, controlling, and demanding, interfering with interpersonal relationships
Dependent personality disorder	Characterized by a pervasive feeling of incompetence and lack of confidence. They cannot make decisions or assume responsibility. These patients are reluctant to take risk and do not show disagreement because of fear of being rejected

dermatologists must conduct a structured medical history including a comprehensive interview, physical examination, and appropriate closure to address patient questions and concerns (Ong et al. 1995).

The interaction between the physician and patients seeking cosmetic procedures is particular. These patients seek to correct imperfections in their physical appearance rather than heal a medical illness (França 2016). All cosmetic procedures must be explained clearly, including possible outcomes and complications to ensure patient satisfaction and prevent false expectations and medicolegal complications, even when the result is not the one expected (Sacchidanand and Bhat 2012).

Table 3 Table 3 Tips to improve the doctor-patient relationship during the encounter. Information taken, modified from (França 2012, 2016; França et al. 2014)

Greet the patient
Be empathic, respectful, and friendly during the interview
Inquire about the patient's concerns using open-ended questions and do not interrupt or rush the patient while speaking
Note the verbal and nonverbal communication signs showed by the patient
Keep eye contact during the interview and avoid crossing the arms
Touch the patient's skin during examination
Make an appropriate closure: summarize the history, give a feedback if required, and ask about further patient concerns or questions

A few tips to maintain an adequate doctor-patient relationship are listed in Table 3.

Patient Expectations

For dermatologist, the ultimate goal of providing therapeutics and esthetic procedures is to deliver a high-quality care to meet patient's expectations. Expectations can be viewed as probabilities, in which expectations are the likelihood of future clinical outcomes or as a value, in which expectations are the patient's desires, necessities, and attitudes (Chang 2012). Bowling et al. says in his review "The measurement of patient's expectations for healthcare," that expectations are the anticipation that given events are likely to occur during or as an outcome of healthcare (Bowling et al. 2012). It is the understanding and meeting of these expectations that increase patient's satisfaction and compliance with the care provided. Furthermore, physicians should know the differences between real and false expectations and how to address them. A real or predicted expectation is the likelihood that an event will occur based mainly on previous expectations; it is expected by both the doctor and the patient (Bowling et al. 2012). Real expectations can be seen as the possible outcomes of a procedure known by the patient from trustful sources. Otherwise, false expectancies are hopes or desires regarding the procedure; they are ideals, based on beliefs and are usually seen in inexperienced patients influenced by doubtful sources (Bell et al. 2002). Expectations are difficult to evaluate as they are complex beliefs, perceptions based on previous experiences, cognitive processes, and social learning (Bowling et al. 2012). They are strongly influenced by cultural backgrounds, hopes, outcomes of previous procedures, and information acquired from different sources, such as internet, family, friends, etc. (Webb and lloyd 1994; França et al. 2014).

Cosmetic dermatologists must know that their patients have high expectations. Thus, cosmetic dermatologists must perform the cosmetic procedure as accurate and safe technically speaking in order to fill patient's expectations and create a trustful relationship (França 2016). Physicians must know the patient's experience with previous cosmetic procedures and their outcomes, backgrounds, and how the patient acquired information about the procedure (Šitum and Buljan 2010). The dermatologist can avoid unrealistic expectation by providing clear information regarding the procedure, including possible outcomes and complications, and solving the patient's concerns and doubts about it (França et al. 2014). Finally, if false expectations are present, the dermatologist must calmly and directly explain how the patient is wrong.

The Difficult Patient

The difficult patient is a common figure of everyday care for physicians. These patients account for up to 15% of all patients and are more likely to present mental disorders (Lin et al. 1991; Haas et al. 2005). Han et al. found that these patients are almost twice as likely to have a psychiatric diagnosis, such as somatoform disorder, anxiety, depression, and body dysmorphic disorder, compared to non-difficult patients. Factors such as patient's expectations and cultural background might hinder the doctor-patient relationship as well as the doctor's overwork, knowledge of mental disorders, and stress (Hahn et al. 1996).

Managing a difficult patient can be challenging for many doctors as physicians are not trained to

Table 4 Tips to improve management of difficult patients. Information taken, modify from (Haas et al. 2005)

Suggestion	Goal	What the physician can say or do
Show empathy	It will help patients to focus on solutions and not in problems	"I can imagine what you are going through," "I can imagine your pain or frustration"
Listen carefully	Paying attention to the patient without interruptions will help the doctor to determine the patient's real concerns, increasing patient collaboration and willingness to solve the problems	Do not interrupt the patient while speaking. Keep eye contact always. Summarize the patient's concerns
Focus on solutions and not in problems	Doctors should focus on finding different ways to solve problems. This will divert the discussion toward solutions and not problems	Keep a positive attitude. Encourage the patient to recognize and solve the problem
Improve partnership with the patient	Calmly point out that the relationship is not ideal, and offer ways to improve it	"Tell me how you feel about the care you are receiving from me." "Do you have any problem with the care I am providing?"
Discuss the process of care	Establish why the patient is looking for care State you are here to help him Talk about expectations and if unrealistic address them	"I am here to help you." "We will work together to find the best solution"

provide a proper management of these patients during medical school and afterwards (França 2016). It can lead to physician frustration and burnout interfering with the doctor-patient interaction. The approach of a difficult patient should begin by doing a personal feedback, which includes ensuring own well-being, improving knowledge about mental disorders, and evaluating communication skills (Vanderford et al. 2001; Haas et al. 2005). It is essential to carefully listen to the patient, focusing on patient's concerns and questions (Lang et al. 2000). This will help the physician to develop specific techniques to improve care of difficult patients. Some tips are listed in Table 4.

Referring the Patient

In the general medical practice, about 30% of patients have a psychiatric disorder (Bronheim et al. 1998). Even though it is proven that these patients benefit from a referral to a psychiatrist or psychologist, many of them are reluctant to be referred. The difficulty of achieving a referral involves many factors; some of them are attributed to the patient and some to the doctor. When talking about the patient, social stigmatization is a factor of major concern. Psychiatric patients are usually considered embarrassing, distrusted, and worthless by society, thereby avoiding psychiatric aid not to be feared or disliked (Bursztajn and Barsky 1985).

Other factors that play a role in rejection of referrals are listed below (Bursztajn and Barsky 1985):

- Impact on self-esteem: Patients believe that going to a psychiatrist means there is a defect that must be "fixed" on them. They see themselves as weak and disturbed.
- The relationship between mind and physical: Patients do not believe that their physical symptoms can be related to psychological problem. These patients believe that there have to be a physical cause of their physical symptoms. Thus, they do not understand why they are being referred to a psychiatrist or psychologist.
- Belief that referral means "rejection by the doctor": For many patients, there is an implicit sense of "rejection" secondary to a referral. This misunderstanding can be intensified by the doctor attitude. A broken doctor-patient relationship strengthens this misconception.
- Always refer to the same doctor: It is important to have a confident psychiatrist or psychologist. This allows a better understanding between the dermatologist, the psychiatrist, and the patient.

- No training in psychiatric diagnosis: Doctor's lack of knowledge about psychiatric condition tampers opportunity to a referral. Many doctors still think that for every physical sign or symptoms must be a physical cause and no psychic condition is allowed.

The doctor-patient relationship is the keystone to create a trustful relationship (França et al. 2014). This allows the patient to openly discuss his/her concerns and feelings about the referral. Physicians should propose the referral in a direct manner, clearly explaining the reasons and carefully listening to the patient's response (Bursztajn and Barsky 1985). The best way to deal with social stigma is being empathic, acknowledging the patients concerns, and focusing in the patient's most feared consequences, specially, if they come from family or friends as they can be addressed easier (Bursztajn and Barsky 1985). Also, doctors should clarify that referring the patient does not mean rejection, and reassure that the patient can still count on the physician.

Finally, a dermatologist trained in psychodermatology must be part of the cosmetic medical practice. It will make it easier to refer those patients that are reluctant to see a psychiatrist or psychologist due to the reasons described above. The psychodermatologist, when available, should be able to manage these cases.

Conclusions

The interest for psychodermatology and the new science cosmetic psychodermatology is rapidly growing. Several researches are being developed to better understand cosmetic patients. These patients are particular, they are looking to correct or improve their appearance rather than cure a medical illness, and many psychological and external factors influence how they perceive their psychical defects. Also, a number of psychiatric disorders have shown to be more common in the dermatologic and cosmetic practice than general medical practice. In such cases dermatologists must work closely with a physician with expertise in mental health care to provide the best care and avoid unnecessary and harmful cosmetic procedures.

The dermatologist must be trained to explore the psychological aspects of patients seeking cosmetic procedures, beginning with a pleasant and trustful conversation with the patient, devoting time to carefully listen to the patient's motivations, concerns, expectations, cultural backgrounds, and previous experiences with cosmetic procedures. Accordingly, dermatologist should not only be trained to perform the most accurate and safe cosmetic procedure, but to see each patient as unique, with its own fears and concerns, looking to be treated as a human being. This will create a good doctor-patient relationship, which is essential for the best medical practice and to achieve full satisfaction.

Take Home Messages

1. Cosmetic psychodermatology is a new science created to study the relationship of psychiatric conditions on patients seeking cosmetic procedures.
2. Cosmetic dermatologists must be trained to perform a brief psychological evaluation prior to cosmetic procedures in order to recognize psychiatric disorders in this diverse population.
3. The prevalence of psychiatric disorders is high in the dermatologic practice. Among them, body dysmorphic disorders are one of the most common disorders, and dermatologists must promptly recognize and refer these patients for appropriate treatment.
4. The doctor-patient relationship is the keystone of the general medical practice. Dermatologists must be trained to establish a good relationship when facing difficult patients. Prompt referral to a psychiatrist or psychodermatologist is essential for psychiatric patients.
5. A psychodermatologist must be part of the cosmetic medical practice. They will provide adequate treatment for patients seeking cosmetic procedures with psychiatric disorders.

Cross-References

- Anamnesis and Physical Evaluation
- Approach in Photodamaged Skin, Melasma, Acne, and Rosacea

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Evaluation and Classification of Aging

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Abstract

When we perceive beauty as a whole, we must consider that several structures are added to its concept. The attractiveness is a result of various features of the face, neck, hair, and body that make an individual be considered beautiful or handsome. In this chapter, we discuss the concept of attractiveness of the face, neck, and hair. Each of these characteristics has a role in the aging process.

Keywords

Aging evaluation • Skin aging • Muscular action • Fat compartments • Bone remodeling of the face • Neck aging • Aging classification

Contents

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Introduction

The billion-dollar revenues of many companies in cosmetics worldwide remind us of the well-known stereotype of the Greek poet Sappho "what is beautiful is good," a tangible proof of the preeminent role of beauty in our society (Coma et al. 2014). Attractiveness is frequently recognized as a desirable personality trait, and surveys show that, in general, the face cannot be seen as an isolated issue in the real world (Saegusa et al. 2015). For the perception of beauty as a whole, it is necessary to integrate not only the face as a single aesthetic unit of attraction but also characteristics such as the surrounding hair, the teeth, skin texture, position of the eyebrows, symmetry, and the neck, which result together to what we call beauty.

In recent decades various techniques have been developed to restore the loss of facial volume and improve the signs of aging. The desire for rejuvenation has led to the development and

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improvement of many substances including fillers and botulinum toxins. Dealing with a patient that is seeking a cosmetic improvement of the face, the dermatologist must be able to evaluate the quality and position of the subcutaneous tissues, understand the aging process, as well as choose adequate techniques for the treatment of the subject to achieve the best aesthetic result (Carruthers and Carruthers 2005).

Aging Process

We will address the aging process by describing the characteristics that shape the perception of beauty and, that as time passes, will result in what we might call unattractive features.

To facilitate our understanding, we have divided these characteristics into aesthetic units: (1) the face, (2) the neck, and (3) the hair (Diagram 1).

The Face

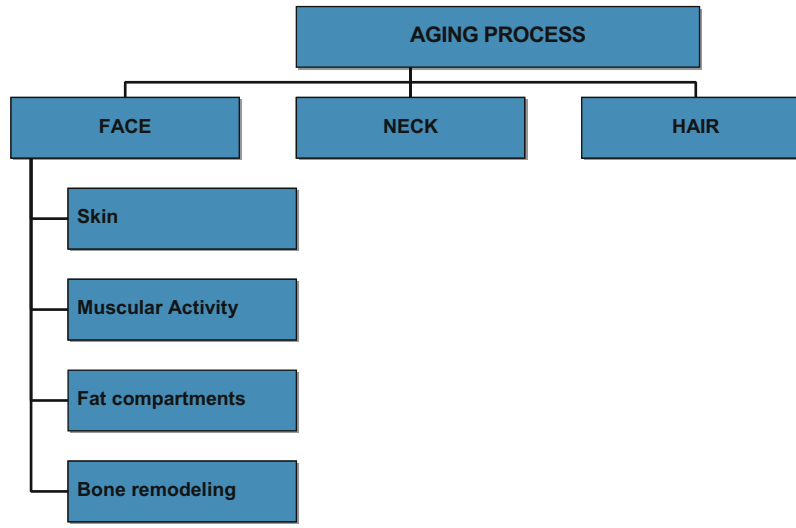
In the aging process of the face, we describe characteristics of the structural changes of the skin, muscular activity, fat compartments, and bone remodeling, which over the years result in the squaring of the face (Coimbra et al. 2014).

Structural Changes of the Skin

Signs of aging in the skin can be classified into four main categories: wrinkles/texture, the lack of firmness of the cutaneous tissues (ptosis), vascular diseases, and pigmentation heterogeneity. Throughout one's entire life, the skin will change in its appearance and structure not only because of the chronological and intrinsic processes but also due to various external factors, such as gravity, exposure to ultraviolet rays, and high levels of pollution, or lifestyle factors which have important and obvious effects on skin aging, such as diet, smoking, diseases, or stress. The effects of these external factors lead to the progressive degradation of integument which appears with different kinetics (Flament et al. 2013).

Flament and collaborators created a descriptive atlas of skin aging and understood it as a solution for specifying extrinsic influence. Twenty-two clinical signs are used to describe and evaluate facial aging, wrinkles and skin texture, tissue laxity, pigmentation, and vascular manifestations and disturbances (Flament et al. 2013). This study

Diagram 1 Esthetic units



seems to confirm that the heterogeneity of pigmentation is a sign of pure photoaging, while tissue laxity is essentially a result of chronological aging. Vasculopathy diseases can be considered as a precursor of future photoaging. Wrinkles and skin texture are influenced by both extrinsic and intrinsic aging, depending on the individual's behavior vis-à-vis the sun, the sun being mainly responsible for premature aging of the face (Flament et al. 2013).

The clinical signs of aging are essentially influenced by extrinsic factors, especially exposure to the sun. In fact UV exposure seems to be responsible for 80% of the visible signs of aging (Flament et al. 2013). It is necessary to consider environmental exposure, nutritional condition, and genetic background to assess the individual aging process. The physical properties, including the water content in the skin, barrier function of the skin, and mechanical firmness/elasticity, seem to be responsible for the smooth aging of the skin (Miyamoto et al. 2011).

With chronological aging, all the cells of the skin begin to produce an excessive amount of free radicals – unstable molecules of oxygen which in ideal circumstances are removed by antioxidants within the skin cells occurring naturally. The free radicals that are generated cause damage to the cellular membranes, proteins, and the DNA. These free radicals may break down a proteic substance in the conjunctive tissue (collagen) and liberate chemical substances that cause inflammation at the skin. It is a combination of these cellular and molecular events that lead to the skin aging and wrinkling (Miyamoto et al. 2011).

The thinning of the epidermis, solar elastosis, and disorganization of the dermal collagen in skin aging are the results of photodamage and smoking which increase the production of intermediary intracellular oxidants (Miyamoto et al. 2011; Guyuron et al. 2009; Hinderer 1993; Kovacs et al. 2010; Varani et al. 2001). Solar elastosis is a term used to describe the histological appearance of the photoaged dermal extracellular matrix. This condition is marked by an accumulation of amorphous material and abnormal elastin material and a reduction of the volume and disorganized variety of collagen fibrils (Elias and Ghadially 2002; Babamiri and Nassab 2010; Lewis et al. 2004; El-Domyati et al. 2002). It is assumed that this elastin abnormal results lead to its degradation through a chronic inflammatory condition (Elias and Ghadially 2002). The other main components of the extracellular matrix, glycoproteins and glycosaminoglycans (GAGs), tend to decline with age, but ironically they are increased in photoaged skin (Miyamoto et al. 2011; Hinderer 1993; Kovacs et al. 2010; Varani et al. 2001; Lewis et al. 2004; El-Domyati et al. 2002; Schlessinger et al. 2011; Berlett and Stadtman 1997; Rittié and Fisher 2002; Young and Woodside 2001).

Ultraviolet A (UVA) and ultraviolet B (UVB) radiation cause direct and indirect damage to the skin. The two most significant chromophores to the UV spectrum in the skin are the DNA and the urocanic acid. Although UVA can induce changes in the DNA directly, its main path of cellular damage is indirect, that is, through the creation of reactive oxygen (singlet oxygen) and various metalloproteinase radicals (Varani et al. 2001; Elias and Ghadially 2002; Babamiri and Nassab 2010; Lewis et al. 2004; El-Domyati et al. 2002; Berlett and Stadtman 1997; Rittié and Fisher 2002; Young and Woodside 2001) which combine to degrade the extracellular collagen. This process leads to an increased oxidative stress which contributes to the degradation of the surrounding collagen although there is an increase of elastin levels (Miyamoto et al. 2011).

It is important to remember that UVB light is almost completely absorbed by the epidermis, and dermal photodamage is almost exclusively caused by UVA. Radiation has also been responsible for increasing angiogenesis and probably contributes to the telangiectasia seen in photoexposed skin (Miyamoto et al. 2011).

In contrast with the epidermis, in the dermis the histological picture of photodamage at the cellular level is a chronic inflammation. Fibroblast and Langerhans cells are reduced and surrounded by abundant inflammatory infiltrate. Interestingly, other important components of the extracellular

matrix, glycoproteins and GAGs, tend to decrease with age, but they are increased in photoaged skin. However, the increased GAGs are not found in the papillary dermis, as is expected; instead of this, they are deposited in the reticular dermis within the elastotic material and are not able to regulate dermal hydration, leading to dehydration of the skin and an appearance similar to the leather (Miyamoto et al. 2011; Libertini et al. 2014).

The tension lines of the skin result from the multiple interactions of extrinsic and intrinsic factors. The intrinsic factors do not depend on external factors, as they reflect genetics personal profile. They consist of inherent properties of extensibility, elasticity, and tension that are associated with the biostructural components of the skin. These structural elements consist of dermal collagen and the elastic tissue. With the aging process, the collagen begins to increase the cross-linking, with its volume and elasticity being reduced. The elastic fibers are more abundant in the dermis of the face than in the scalp and, therefore, are responsible for maintaining the static tension of the skin and for restoring the deformed collagen to the original state. With aging, and especially with prolonged solar exposure, the elastic fiber structure and function deteriorate, progressively losing the ability to return to the original length, which results in the loss of firmness of the skin (Salasche et al. 1988).

Extrinsic factors such as facial mimic muscles are directly inserted into the skin, leading to a continuous tension even in repose. Over time they produce an elongation of the collagen in the direction of the muscular traction. In infancy, the elastic tissue maintains its configuration, and these changes are not very apparent. With aging the skin loses its elasticity; its elongation starts to be noticed with the redundant skin directed into furrows and wrinkles. The linear wrinkles result from the union of multiple fibers of the superficial muscular aponeurotic system (SMAS) with the dermis elongating the skin and reducing the tension in the direction of the movement of the facial muscles. The lines of tension of the skin are perpendicular to the sum of the force vectors of muscular action. The reduction of tension, the increase in the elongation of the collagen fibers, and the progressive reduction of elastic tissue create these lines that become exacerbated with progressive aging and/or with solar damage (Salasche et al. 1988). In this way, such factors taken together lead to the increase of cutaneous flaccidity and excessive facial and neck skin.

Muscular Action

In youth facial mimetic muscles have a curvilinear contour, presenting anterior convexity on the surface which makes them project outward. This reflects a curve in the fat compartment subjacent to the deep face of these muscles which acts as an efficient mechanical gliding plane. The amplitude of the muscle movement is also greater. Over time the convex contour becomes planar, and the underlying fat is expelled from behind the muscles, resulting in an increase in superficial fat (Pessa and Rohrich 2011).

The frontalis muscle presents little underlying fat. During contractions, maximum pressure is exerted in its central functional area, where the elevator and depressor forces converge, producing over time central horizontal bone resorption with upper (frontal collisions) and lower (superciliary arch) convexity (Louran et al. 2007).

The muscles of the glabella region are responsible for the main noticeable alterations of aging in the upper third of the face, as they have a strong depressant action. The corrugator muscles, procerus, depressor supercilii, and the upper portion of the orbicularis oculi muscles make part of this region. Their contractions contribute to the facial appearance of tiredness and boredom, as well as to the increase of skin in the upper palpebral region and the displacement of fat pads in the same region (Louran et al. 2007).

The contractions of the orbicularis oculi muscles are also responsible for the facial aging, leading to the protrusion of the orbicular fat, resulting in palpebral sagging. They also contribute to the descent of the caudal eyebrow, to the onset of periocular rhytids (crow's feet), and to the increase of the cutaneous ptosis in the palpebral

region. Repeated contractions of the corrugator supercilii muscle expel the deep fat compartment, contributing to the erosion of the orbital bone (Louran et al. 2007).

The levator muscle of the upper lip and the nasal ala corresponds to an association of two other muscles: one that is superficial (levator of the nasal ala) and the other that is one deep (levator of the upper lip). Its repeated contractions expel the underlying fat inferiorly into the canine fossa and the superficial fat into the nasolabial fold, flattening the convexity of the anterior malar region. Over time, a depression, which increases visibly when smiling, appears above the nasolabial fold in the paranasal area. The deep fat, which in youth is located between the cutaneous insertion of the levator muscle of the nasal ala and the pyriform orifice, is also pushed to the nasolabial fold (Louran et al. 2007).

During the aging process, the zygomaticus major and minor muscles expel the deep underlying fat located in the lower region, leading to the emptying of the jugal area. The facial mimic muscles are particularly strong in the periorbital and perioral areas. Their repetitive contractions, combined with the increase of the muscle tonus at rest, not only expel the underlying fat but also exert constant pressure on the bone, contributing to its erosion. Repeated contractions of the orbicularis oris muscle lead to the appearance of perioral rhytids, besides aiding in the reduction of the volume and loss of the lip contour.

Repeated contractions of the depressor anguli oris muscle, combined with the elevation produced by the mentalis muscles, expel the underlying fat toward the upper middle cervical region, increasing the excess of the skin. Furthermore, the resting tonus of the depressor muscles of the mouth and of the angle of the mouth increases over time, depressing the commissure and deepening the labiomental fold (Louran et al. 2007). Below the mandible, contractions of the anguli oris muscle of the facial mimics stimulate the platysma muscle, expelling the deep fat anteriorly.

In youth the platysma has the configuration of an hourglass, simulating a narrower "waist" between its lower transversal origin and the upper transverse insertion that helps to define the cervicomandibular angle. With aging, its tonus at rest increases, and there is a shortening of the vertical length, leading to the formation of anterior bands that erases the cervicomandibular angle. The contractions of the platysma muscle over time expel the deep fat anteriorly in the submental region.

Fat Compartments

Facial fat is divided into different separate compartments that are limited by distinct anatomical units with their own vasculature (Tables 1 and 2).

Traditionally, facial fat compartments are divided into a superficial and a deep layer in relation to the skeletal system and the muscles of facial mimics. However, the division of these two layers of distinct compartments is not so intuitive (Wan et al. 2013).

In 1996 and 2005, Gosain et al. (Gosain et al. 1996; Rohrich et al. 2008) divided the fat of the superficial cheek into medial and lateral masses based on their relationship with the underlying mimetic muscles on MRI (Wan et al. 2013).

It was not until 2007 that Rohrich and Pessa developed an anatomical and reproducible study of 30 cadaveric dissections concerning the division of the facial fat compartments. They injected methylene blue dye into hemifacial cadaveric specimens which allowed them to delimitate the natural septal boundaries and the fat compartments (Rohrich and Pessa 2007).

Table 1 Superficial fat compartments of the middle third of the face. The nasolabial fat, the superficial medial cheek fat, and the infraorbital fat form part of the malar fat

Superficial fat compartments of the middle third of the face	
Nasolabial fat	NLF
Superficial medial cheek fat	SMCF
Medium cheek fat	MCF
Lateral-temporal cheek fat	LTCF
Infraorbital fat	IOF

Table 2 Deep fat compartments of the middle third of the face

Fat compartments of the deep medial cheek fat (DMCF)		Infraorbital fat compartment of the eyes
Medial	**Lateral**	Orbicularis oculi muscle deep to the lower lid
Deep and medial to the NLF	Deep to the SMCF	Densely adhered to the periosteum
Limited by Ristow's space, inferior border of the maxilla	Medial to the buccal extension of the buccal fat pad compartment	Divided into lateral and medial

Table 3 Fat compartments[a]

Nasolabial fat compartment
Fat compartment of the cheek 1. Medial 2. Middle 3. Lateral-temporal
Frontal-temporal compartment 1. Frontal-central 2. Middle temporal 3. Lateral-temporal
Orbital fat compartments 1. Superior orbital 2. Inferior orbital 3. Lateral orbital
Mentum fat compartment

[a]Rodrich and Pessa (2007)

In another study, Rohrich and Pessa described the nasolabial fat compartments, malar, frontal, temporal, orbital, and the mentum. The descriptions of the compartments (Rohrich et al. 2008; Rohrich and Pessa 2007, 2009) (Table 3) and figure follow below:

The nasolabial fat compartment is located anteriorly to the medial cheek fat pad and is adjacent to the mentum fat. The orbicularis retaining ligament (ORL) represents the upper border of the compartment and is located medial to the deep fat of the infraorbital fat compartment, and its lower border is the zygomaticus major muscle that adheres to this compartment.

There are three distinct cheek fat compartments: the medial, the middle, and the lateral-temporal cheek fat. The medial cheek fat compartment is located laterally to the nasolabial fold. This compartment is limited superiorly by the orbicularis retaining ligament and laterally by the orbital compartment. The lower limit is set by the fat of the mentum. The middle cheek fat compartment is located in the midportion, anterior and superficial to the parotid gland. In its upper limit, it adheres to the zygomaticus major muscle. There is a confluence of septa in this area, where the three compartments are located and form a dense adherent zone where the zygomatic ligament is described (Rohrich and Pessa 2007; Furnas 1989). The middle cheek fat compartment is confined between the medial compartment and its septal limits, fusing within a dense facial system. The area where the medial fat is confined to the middle fat corresponds to the location of the parotid masseteric ligament (Rohrich and Pessa 2007; Stuzin et al. 1992). The lateral-temporal is the most lateral cheek compartment. The fat is located immediately superficial to the parotid gland and connects the temporal fat with the subcutaneous cervical fat.

The forehead and temporal regions consist of three fat compartments. The central compartment is located in the midline of the forehead. It is confined between the medial temporal compartments and, at its lower border, the nasal dorsum. The lateral limit is likely a septal barrier and can be referred to as the central temporal septum. The middle temporal fat compartment is adjacent to the central forehead compartment, and both lie at the side of the fat pad of the central forehead. Its inferior border is the orbicularis retaining ligament, and its lateral border corresponds to the superior temporal septum. The compartment of the lateral-temporal cheek was described above. It is connected with the lateral forehead, lateral cheek, and cervical fat pads.

The orbital fat compartments are also divided into three types of fat pads around the eye. The superior compartment is limited by the orbicularis retaining ligament and runs around the superior orbit. The orbicularis retaining ligament is a circumferential structure that spans the superior and

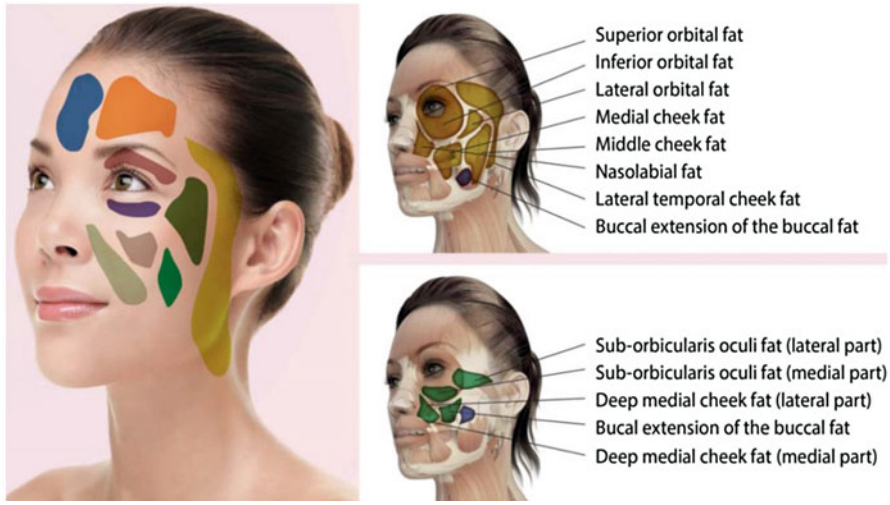


Fig. 1 Fat compartments of the face (Adapted from Gierloff and cols)

inferior orbit and fuses in the medial and lateral canthus. The inferior orbital fat is a fine subcutaneous layer which lies immediately below the inferior tarsus. Its inferior limit is the orbicularis retaining ligament (ORL) or the malar septum. The medial and lateral extension extends until the ocular canthus. The lateral orbital fat compartment is the third orbital fat pad. Its superior border is the inferior temporal septum, and its inferior limit is designated by the superior cheek septum. The zygomaticus major muscle is once again observed adhering to the compartment. The transition of the zygomaticus major muscle plays an important role, releasing the soft tissues and trying to raise the medial fat from the mentum.

The chin fat compartment is separated from the nasolabial fat (NLF) and adheres to the depressor muscle of the mouth commissure. The medial limit of this compartment is the depressor muscle of the lip, and the inferior limit is determined by the membranous fusion of the platysma muscle. The point of fusion between the two muscles lies in the mandibular retaining ligament.

Coleman et al. also described different fat compartments, subdivided into regions: periocular, temporal, perioral, and mandibular regions, middle third of the face, and the cheek (Coleman et al. 2009).

Through a tomography study employing contrast on the faces of cadavers, Gierloff et al., in 2012, put forward a different classification of the fat compartments mentioned here. The compartments were divided into fat in the middle third of the face constituted by two layers (superficial and deep) and the paranasal region, divided into three anatomically different layers (Gierloff et al. 2012) (Fig. 1).

The superficial layer is composed of nasolabial fat, medial and middle cheek fat, the frontal-temporal compartment, and three orbital compartments. The deep layer consists of infraorbicular fat and deep medial cheek fat (DMCF). Three distinct fat compartment layers are found in the pyriform aperture, where the compartment is located posterior to the medial part of the deep medial cheek fat (Gierloff et al. 2012).

The nasolabial compartment is subcutaneous and oval in shape. Its superior border is located in the inferior contour of the orbit, and its inferior extension is adjacent to superior mentum fat. The compartment is limited laterally by the middle malar fat and infraorbital fat. The medial border is formed by the maxilla and the lateral compartment of the upper lip.

The medial cheek fat compartment is lateral to the nasolabial compartment. The inferior limit is

established by the mentum fat and by the buccal extension of the buccal fat. The compartment is limited laterally by the fat of the middle cheek region and by the lateral orbital compartment. The posterior border is formed by the orbicularis oculi muscle, the deep medial cheek fat, and the buccal fat pad.

The middle cheek compartment is located anteriorly to the frontotemporal compartment and laterally to a line perpendicular to the lateral orbital border. The anterior limit is the fat of the malar region and of a small part of the buccal fat pads. The superior border is the lateral orbital compartment.

The deep medial cheek fat compartment is subdivided into medial and lateral parts. The medial part is located below the nasolabial compartment but extends farther medially. It does not rest immediately on the periosteum of the maxilla, being limited posteriorly by a small triangular compartment. The lateral portion limits the superficial medial cheek fat (SMCF). Its superior limit is with the infraorbital fat and the lateral and the buccal fat. The compartment rests medially on the deep medial cheek fat and laterally on the maxilla.

The infraorbital fat is divided in two; the medial part is located above the periosteum of the maxilla and its inferior portion above the lateral part of the deep medial cheek; its medial part of the infraorbital fat is covered by the nasolabial fat and medial cheek. The lateral part of the infraorbital fat is located below the lateral orbital compartment and the medial cheek fat (Gierloff et al. 2012).

The buccal fat compartment plays an important role because it extends from the deep premaxillary space to the inferior superficial subcutaneous plane of the zygomatic bone. The buccal extension of the buccal fat pad compartment is considered to be part of the posterior lobule. However, Gierloff et al. observed in 29% of the cadavers analyzed that the buccal extension of the buccal fat pad can be considered a distinct compartment, as it has a limited anatomical site, in this case a third layer (Gierloff et al. 2012). This compartment is located inferiorly to the zygomatic bone and anteriorly to the mandibular ramus around the masseter muscle. Only one small portion of the compartment is located in the premaxillary space. The subcutaneous extension of this compartment confines the medial cheek fat; the deep medial, central, and infraorbital fat of the mentum; and the pre-masseter space and can provide support to all these fat compartments (Pessa and Rohrich 2011).

The orbital region is divided into superior, inferior, and lateral compartments. The inferior orbital fat compartment is located in the subcutaneous plane, beneath the middle portion of the orbital bone and its inferior border following the same inferior course. The limit of the inferior compartment is the medial, central, infraorbital, and nasolabial cheek fat. The superior orbital fat compartment is located immediately beneath the skin of the upper eyelid. The superior border follows the course of the orbital bone, and the lateral portion is located at the lateral margin of the orbital bone. The inferior border of the lateral orbital fat is the medial cheek fat. In the lateral orbital compartment, the superior border is located in a virtual line between the superior orbital contour and the temporomandibular joint articulation. The inferior portion of the compartment overlaps the lateral part of the suborbicularis fat pad. The lateral orbital fat is limited laterally by the temporal cheek fat (Gierloff et al. 2012).

Alterations related to the reduction of volume, atrophy, and migration to lower regions of the face of these fat compartments probably constitute the main factors of the structural changes of the face involved in the aging process.

Recently Wan et al. (2014) analyzed 63 dissections of the hemiface in cadavers and observed three principal alterations:

1. The adipocytes in the superficial fat compartments were greater than when compared with the adipocytes of the deep fat compartments.
2. The size of the adipocytes in the nasolabial fat compartments (NLFC) and the deep medial cheek fat (DMCF) in men is significantly smaller than when compared with women.

3. The size of the adipocytes in the nasolabial fat compartment (NLFC) in patients with a normal body mass index (BMI) is significantly greater in women than in men. This supports the clinical and anatomical observations that suggest there are morphological differences between the superficial and deep fat compartments, specifically selective atrophy of the deep fat compartments of the elderly. This finding may be clinically important for the effects of volumetric facial rejuvenation.

Bone Remodeling of the Face

The areas with a predisposition to bone remodeling correspond to the mobile parts of the face, especially the superomedial and inferolateral areas of the orbit, pyriform aperture region of the nose, mentum, and particularly the maxilla, in which this process is more prominent. The alterations that occur with the aging process consequently produce an increasing protrusion of the glabella, expansion of supraorbital wrinkles, lateral translation of the orbit, an increase in depth, lateral expansion of the cheeks, and an increase in size of the nose and mentum.

The medial fat pad of the orbit also becomes more prominent with age, possibly as a result of the resorption of the superior border of the orbit. The middle malar region presents more complex alterations of the soft tissue with age. The development of the tear trough, malar fat, and nasolabial folds can be, to a significant degree, attributed to the loss of some fat or age-related ptosis.

The decreased projection of the maxilla contributes to the increase of the pyriform aperture, due to the fact that there is a weakening of the bone support of the nose, as well as of the upper lip, resulting in this way in the ptosis of the centrofacial region and elongation of the space between the nose and the upper lip.

The maxilla is the bone that undergoes the greatest remodeling with aging, the consequences of which are perceptible in the cheeks. The maxillary bone gives origin and function to other bones that form the orbit. In youth it expands to accommodate the growth of secondary dentition – which develops within the bone – resulting in a great reduction of the volume in its way, especially in its inferior part (Mendelson and Wong 2012).

With aging, the lower third of the face undergoes vertical maxillary shortening, affecting dental and skeletal structures. This negative combination also influences the smile of the patient, as it results in the reduction of the exposure of the upper and anterior teeth. Sometimes, the structural factors of aging are not easily detected due to the compensation offered by the soft tissues, which in young individuals plays an important camouflage role (Meneghini and Biondi 2012; Krogman 1973).

The Neck

In recent years, the neck has been receiving special attention from the aesthetic standpoint, and isolated procedures have been gaining popularity (Larson et al. 2014).

Like the skin of the face, when the skin of the neck ages, all the cells also start producing excessive quantities of free radicals. The free radicals produced cause damage to the cell membranes, proteins, and DNA. These free radicals eventually break down a protein in the connective tissue (collagen) and release chemical substances that cause the inflammation of the skin. It is the combination of these cellular and molecular events that lead to the aging of the skin and to the formation of wrinkles (Miyamoto et al. 2011).

Although the neck is relatively protected by the head, especially by the mentum, and by the hair, it is still a photoexposed area and it is the main cause for the skin aging, associated with the resorption of the fat compartments and muscle activity.

Guerrero Santos observed 30 years ago that elderly individuals with thin necks presented platysmal bands and that the etiology of these bands was muscle dehiscence and laxity.

In a recent study, Rohrich and Pessa described these fat compartments, their relationship with the retaining ligaments, and their clinical significance in the aging process.

Subplatysmal fat was found in three compartments – central, medial, and lateral – based on their anatomical location, fat composition, and studies

using dye injections. The three compartments form a V-shaped mass of adipose tissue, which extends from the lateral mandible to the thyroid cartilage. These compartments may be differentiated by their colors. The central compartment is yellow, whereas the medial and lateral compartments are paler, similar in color to the buccal fat. The subplatysmal fat lies under the platysma muscle and fascia (Rohrich and Pessa 2010).

Larson and collaborators differ slightly from the Rodrich and Pessa study, suggesting a supraplatysmal suprahyoid fat compartment containing 29.7% of the neck fat and a supraplatysmal infrahyoid compartment containing 15% of the fat. However in this study, six subcompartments of the subplatysma were described: (1) central suprahyoid, (2) central infrahyoid, (3) left suprahyoid, (4) right suprahyoid, (5) left infrahyoid, and (6) right infrahyoid (Larson et al. 2014) (Diagram 2).

In a recent study, Larson observed that most of the fat in the neck is found in the superficial layer, supraplatysmal plane (44.7%), whereas one third (30.7%) of the fat in the neck is found in the subplatysmal compartment, deep to the platysma muscle. However, the fat in this layer may vary between 18% and 45% of the total neck fat from person to person. The findings of the study demonstrated that in men the submandibular gland may be relatively larger and the superficial fat relatively lesser than in women (Larson et al. 2014).

The submandibular gland represents the smaller portion of the fat in the neck, but nevertheless, its ptosis contributes significantly to the aging of the neck (Larson et al. 2014). Many times, the aging of the neck is represented as marked medial platysmal bands (Larson et al. 2014).

Hair

The human hair's biological function is to protect the scalp; however it also plays a role in physical attraction and in the perception of beauty. Hair loss, aging hair, seborrhea, and other conditions that affect the health of the hair may be distressing for patients, as it is often considered an important aspect of people's evaluation of their own physical beauty.

External factors, such as sun exposure; smoking; dietary factors; malnourishment of essential fatty acids and vitamins; and chemical products applied to the hair and scalp through shampoos and other treatments may cause damage to existing hair

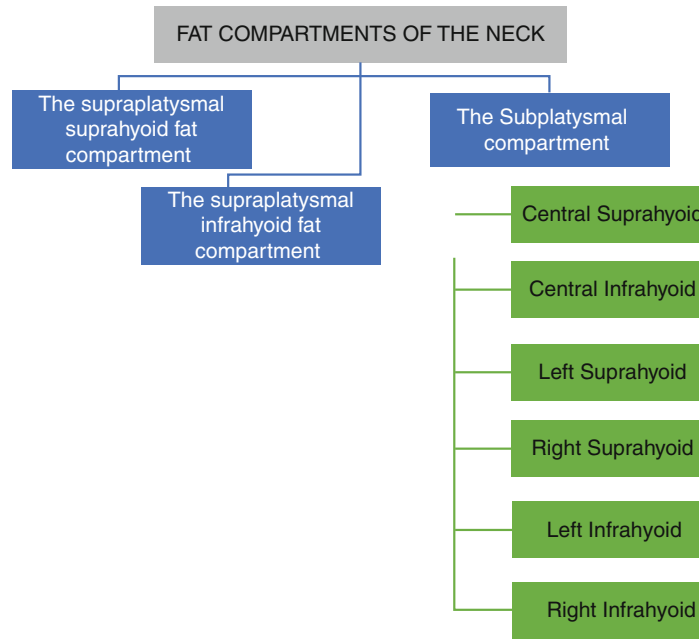


Diagram 2 Fat compartments of the neck

and impair its growth. Hair loss is considered by most people to be an element that affects one of the beauty factors that distinguishes an attractive person (Chiu et al. 2015).

Assessment of the Face

A largely used practice to assess the symmetry and balance of the face is to divide it horizontally into three thirds. The upper third extends from the hairline to the glabella, the middle third from the glabella to the subnasale, and the lower third from the subnasale to the mentum (Carruthers and Carruthers 2005) (Fig. 2).

Different types of facial alteration occur during the aging process. In the upper third, these are related to chronic damage due to ultraviolet light exposure, to intrinsic muscles of facial expressions and their influence on the skin, and to the gravitational changes caused by the loss of tissue elasticity (Carruthers and Carruthers 2005; Salasche et al. 1988; Coleman and Grover 2006). Changes in the middle third result from a combination of photoaging, loss of subcutaneous tissue, loss of skin elasticity, and remodeling of bone and cartilaginous structures.

The orbital septum may weaken over time, allowing for the protrusion of fat in the lower or upper eyelid. However, some people may experience loss of subcutaneous palpebral tissue, causing in this way a sunken appearance to the eyes.

The malar region may be affected by volume loss of the buccal fat pad, which is located between the masseter muscle (anteriorly) and the buccinator muscle (posteriorly).

The nasal tip supporting mechanisms may become inelastic and elongated with age, causing the ptosis of the nasal tip and apparent elongation of the middle third of the face (Carruthers and Carruthers 2005; Salasche et al. 1988; Mendelson and Wong 2012; Coleman and Grover 2006). In the lower third, the alterations are caused by the combination of chronic damage due to ultraviolet light exposure, loss of subcutaneous fat, changes related to the muscles of facial expressions and the neck, gravitational changes caused by the loss of tissue elasticity, and remodeling of bone and cartilaginous structures.

Dentition structure and the resorption of the maxillary and mandible bones may lead to a widespread loss of size and volume. The mentum rotates anteriorly and becomes thinner and more protruded. In addition to the decrease of actual volume in the lips, the ptosis of the nasal tip can

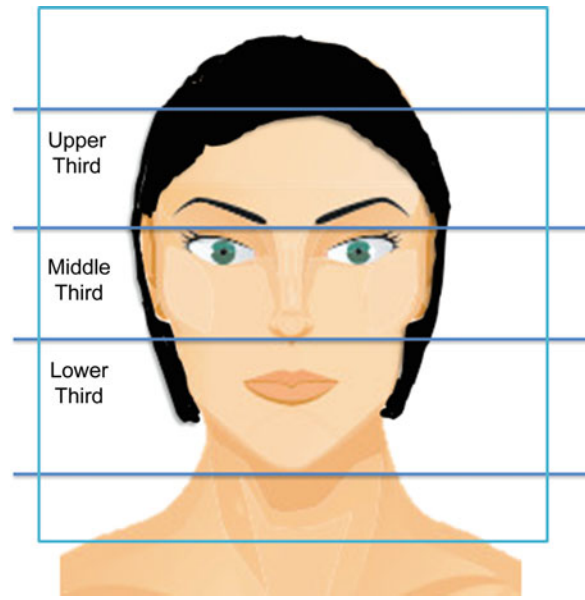


Fig. 2 The upper third extends from the hairline to the glabella, the middle third from the glabella to the subnasal, and the lower third from the subnasal to the chin

also contribute to the reduced appearance of the upper lip (Carruthers and Carruthers 2005; Salasche et al. 1988; Mendelson and Wong 2012; Coleman and Grover 2006).

Facial Squaring

Some authors believe that in adolescence, the face has the shape of a heart or of an inverted triangle and that, with the aging process, this triangle is reversed and, therefore, its base is shifted to the mandibular line. Others, however, believe that all faces have a single shape, similar to that of an inverted trapezoid, with the upper limit being constituted by a line running between the most projected portions of the zygomatic bone and with the inferior limit being defined by a line drawn laterally to the mentalis muscles, approximately in the junction of the depressor *labii inferioris* muscle with the mandible. What varies from one individual to another, both in men and women, are the internal angles of this trapezoid, which can be more or less acute depending on the shape of the face (Coimbra et al. 2014).

Thus, rather than approaching the aging changes in the face by reversing the triangle of youth, authors have noted an increase of the superior angles of the trapezoid accompanied by a discreet shortening of the superior line (resorption of the zygomatic bones) and a decrease of the inferior angles followed by a marked increase in the inferior line of the trapezoid (the facial structures are displaced to the lower third of the face), in such a way that this inverted trapezoid tends to become more square-shaped over the years, regardless of gender, race, or shape of the face (Coimbra et al. 2014).

The Skin

Miyamoto et al. observed alterations of the skin according to age groups and realized that the first alterations of the skin were related to the size of the pores, which notably increases in the years of adolescence. The number of pores, that is, apparent follicles on the skin surface, may increase during the adolescent phase, a period in which the secretion of sebum commences, along with the development of the sebaceous glands and the increase of the rate of sebum production. A peak in the secretion of sebum is seen between 30 and 40 years of age, and after this, the number of pores decreases in a direct relation with the decrease of the sebum secretion. Therefore, attention to the apparent changes in the pores should be given to relatively younger groups, and as there is not much correlation between this alteration and other age groups, this cannot be used as an index for facial skin aging (Miyamoto et al. 2011).

Changes in skin texture are significant at the age of 20. Texture was defined as the roughness of the skin surface due to the presence of skin furrows caused by dry skin.

The texture of the skin tends to increase later in life and, therefore, can be used as an index for aging.

Hyperpigmentation starts to noticeably increase between 20 and 30 years of age and is caused by the overproduction of melanin induced by ultraviolet radiation. However, hyperpigmented lesions take longer to form than the visualization of the surface properties, such as texture, as the melanin pigmentation produced in the melanocytes and its accumulation in the basal layer take time.

Wrinkles noticeably increase from 30 to 40 years of age and reflect structural changes caused by the physical deterioration of the dermal structure, such as elastin lying immediately beneath the epidermis and collagen in the dermal layer (Imokawa 2008; Imayama and Braverman 1989), and may take longer to become visible. Hyperpigmentation and wrinkles increase significantly from the age of 60 and, therefore, may be used as a skin aging index. Attributes that are highly correlated with aging and which are an aging index are hyperpigmentation disorders, wrinkles, and skin texture (Miyamoto et al. 2011).

Men Versus Women

It is also important to note some differences between male and female patients (Antonio and Antônio 2001). Male skin is thicker at all ages (Coimbra et al. 2014). Male cutaneous annexes show a greater activity with men having increased production of sebum and sweat. There are significant differences in the distribution of hairs, as the growth of sexual hair depends on androgens. Androgen-dependent areas include the chin, upper lip, chest, breasts, abdomen, back, and anterior thighs (Keaney 2015).

Subcutaneous structures are important and should be taken into consideration when assessing a male cosmetic patient. The male skull is not only unique in its larger global dimension but also in its unique shape. Men tend to have a large forehead with prominent superciliary arches and glabella (Garvin and Ruff 2012), square orbit, and more prominent mandible. Men have more (Janssen et al. 2000) skeletal muscle mass, including facial mimetic muscles (Weeden et al. 2001), and more vascularization of the face due to the vascular plexus supporting the beard hairs (Moretti et al. 1959). The greater density of facial vasculature makes men more prone to develop bruising from injectables, especially in the lower face (Keaney 2015).

The subcutaneous adipose layer in men is thinner regardless of age (Sjostrom et al. 1972). The subcutaneous fat of the face also exhibits sexual dimorphism. The assessment of facial soft tissue by using three-dimensional (3D) reconstructed models demonstrated that men have less subcutaneous tissue in the cheek area (Codinha 2009; Cha 2013). Women have 3 mm more subcutaneous tissue in the medial malar area when compared with men (Wysong et al. 2013). Clinically, this difference corresponds to more angular cheeks in men (Keaney 2015).

The anatomical variations between genders will result in differences in the aging process. Male facial aging is unique and must be addressed and treated differently. Facial rhytides in men are more severe except in the perioral region (Tsukahara et al. 2013; Paes et al. 2009). The loss of subcutaneous adipose with age results in deeper expression lines in men because of the thicker skin and more prominent facial musculature, unlike women who tend to develop more superficial rhytides. The loss of subcutaneous fullness makes men appear older when compared to women (Keaney 2015; Bulpitt et al. 2001).

Aging Classification

Patients frequently do not have an accurate understanding of the nature of their defects, and they must, before anything else, be educated about the underlying anatomy of their wrinkles (Antonio and Antônio 2001).

Distinction must be made between dynamic and static lines and those changes due to external photodamage, as opposed to those secondary to gravitational and chronological influences. Although these skin imperfections are often combined, their treatments require individualized assessing (Antonio and Antônio 2001).

Besides the type of defect being clearly important, so is its size, depth, and location, as well as the appearance and integrity of the underlying tissues. In 1994 and 1996, Glogau et al. developed a classification system to measure the types of photoaging related to the amount of sun exposure (Table 4).

Table 4 Glogau et al. developed a classification system to measure the types of photoaging related to the amount of sun exposure

Glogau scale	
Type I	Mild photoaging. Mild pigment changes, minimal wrinkles, minimal acne scarring. Light makeup is able to conceal the signs
Type II	Moderate photoaging. Early brown spots, palpable keratosis, nasolabial lines begin to appear, discreet acne lesions. More foundation is needed to cover up signs of aging
Type III	Advanced photoaging. Obvious dyschromia, static wrinkles, acne scars
Type IV	Severe photoaging. Yellow-gray skin color, malignant lesions, widespread wrinkles, acne scars. Makeup makes the skin cake and crack

In 2008, David Shoshani et al. published a new study about the development of a new scale to assess nasolabial wrinkle severity (Shoshani et al. 2008).

In 1996, Fitzpatrick et al. proposed a wrinkle grading system for assessing perioral and periorbital wrinkle severity in a study evaluating the effectiveness of laser treatment in resurfacing photoaged skin. This classification was based on widespread wrinkling, elastosis, and dyschromia, as well as wrinkle depth. Using reference photographs, the wrinkles were classified into one of three classes (1, 2, or 3) and defined as mild, moderate, or severe. Instead of intermediate classes, each of the three main classes was divided into three additional subclasses; these subclasses were represented by photographs of clinical studies.

Table 5 Modified Fitzpatrick Wrinkle Scale

Aging process – Modified Fitzpatrick Wrinkle Scale	
Class 0	No wrinkle. No visible wrinkle; continuous skin
Class 0.5	Very shallow yet visible wrinkle
Class 1	Fine wrinkle. Visible wrinkle and discreet indentation
Class 1.5	Visible wrinkle and clear indentation. Wrinkle depth <1 mm
Class 2	Moderate wrinkle. Clearly visible wrinkle with depth between 1 and 2 mm
Class 2.5	Prominent and visible wrinkle. More than 2-mm and up to 3-mm wrinkle depth
Class 3	Deep wrinkle. Deep furrow; more than 3-mm wrinkle depth

In this study, a Modified Fitzpatrick Wrinkle Scale was proposed for the assessment of nasolabial wrinkles. The four main classes defined to assess wrinkle severity were based on reference photographs together with the descriptions. Instead of subclasses, this scale includes three intermediate classes, in which definitions are based only on descriptions. The objective of this study was to determine the reproducibility and reliability of this scale as a clinical tool to assess nasolabial wrinkle severity in volunteers and patients of the study. The definitions of the entire classes of the scale are in Table 5 (Antonio and Antônio 2001).

Therefore, this relatively simple scale has proved to be a reliable grading system for assessing nasolabial wrinkles. Although efficient enough to rely on four reference photographs, the addition of a series of clear and concise descriptions for each class resulted in greater precision of the assessment process and is likely to be adaptable for assessing other (Antonio and Antônio 2001) wrinkles and furrows.

Carruthers and collaborators developed a five-point photonumeric grading scale of the forehead to objectively quantify the resting (static) and hyperkinetic (dynamic) lines in this region (Fig. 3) (Carruthers et al. 2008a). Following this,

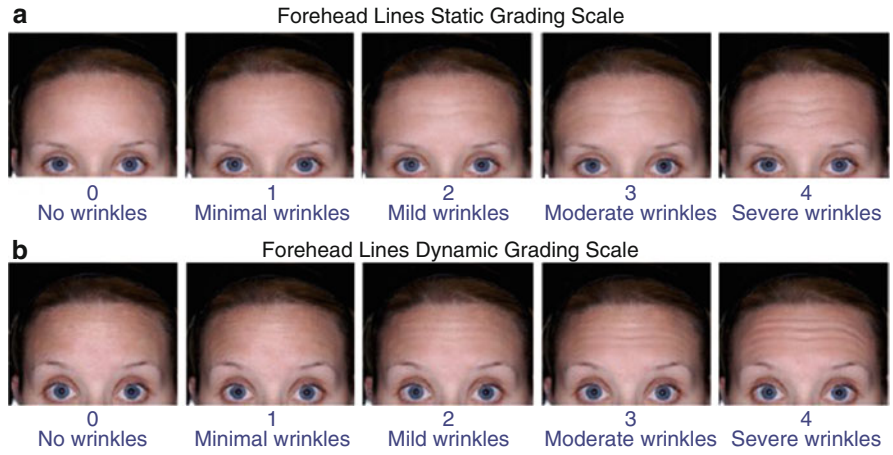


Fig. 3 Forehead lines grading scale by Carruthers: Static lines (**a**); Dynamic lines (**b**)

they developed a measuring tool to assess the melomental folds, a five-point photonumeric grading scale of the marionette lines to objectively quantify the severity of the folds (Carruthers et al. 2008b) (Fig. 4).

Many more scales have been developed with a view to classify certain wrinkles caused by aging, for example, the five-point photonumeric scale to quantify the severity of the nasolabial folds (Monheit et al. 2010) (Fig. 5). In addition to this,

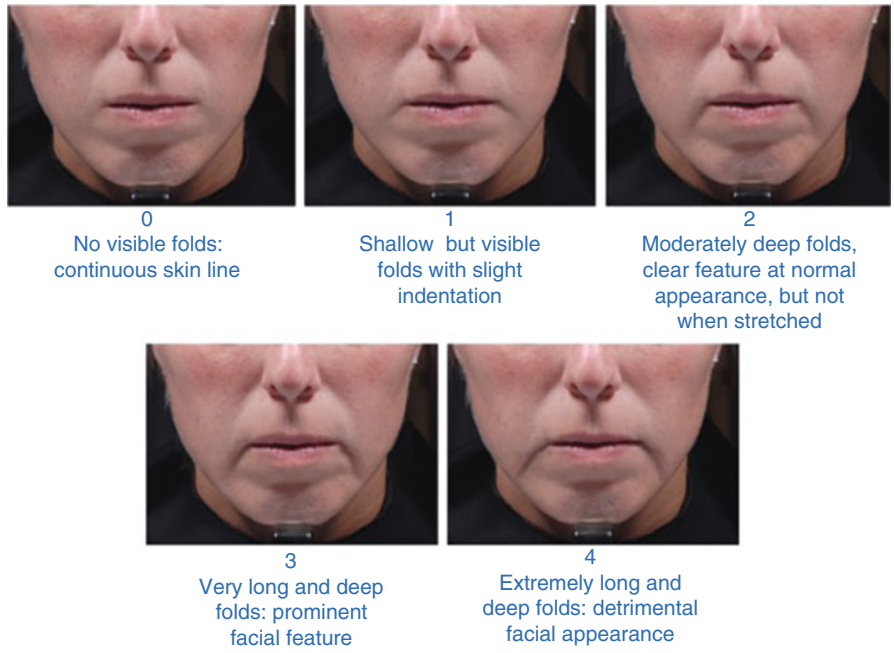


Fig. 4 Scoring of the photonumeric scale for severity of melomental folds by Carruthers

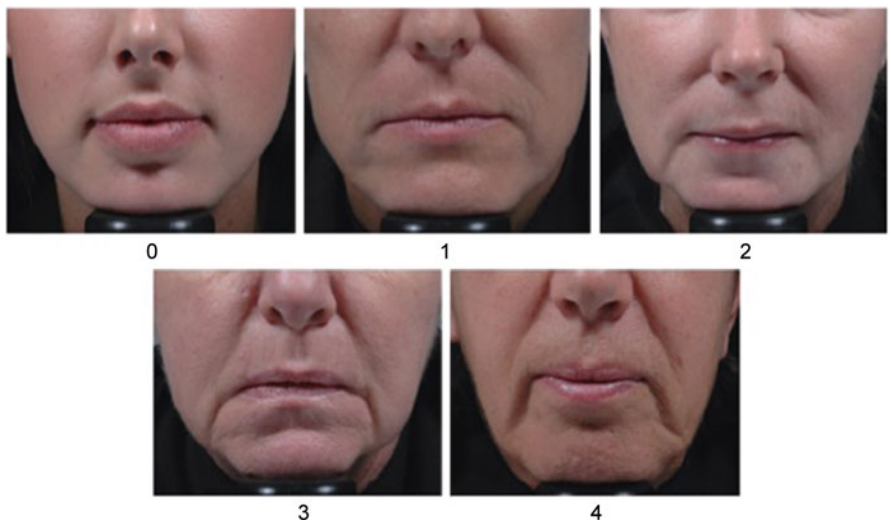


Fig. 5 Five-point photonumeric scale to quantify the severity of the nasolabial folds

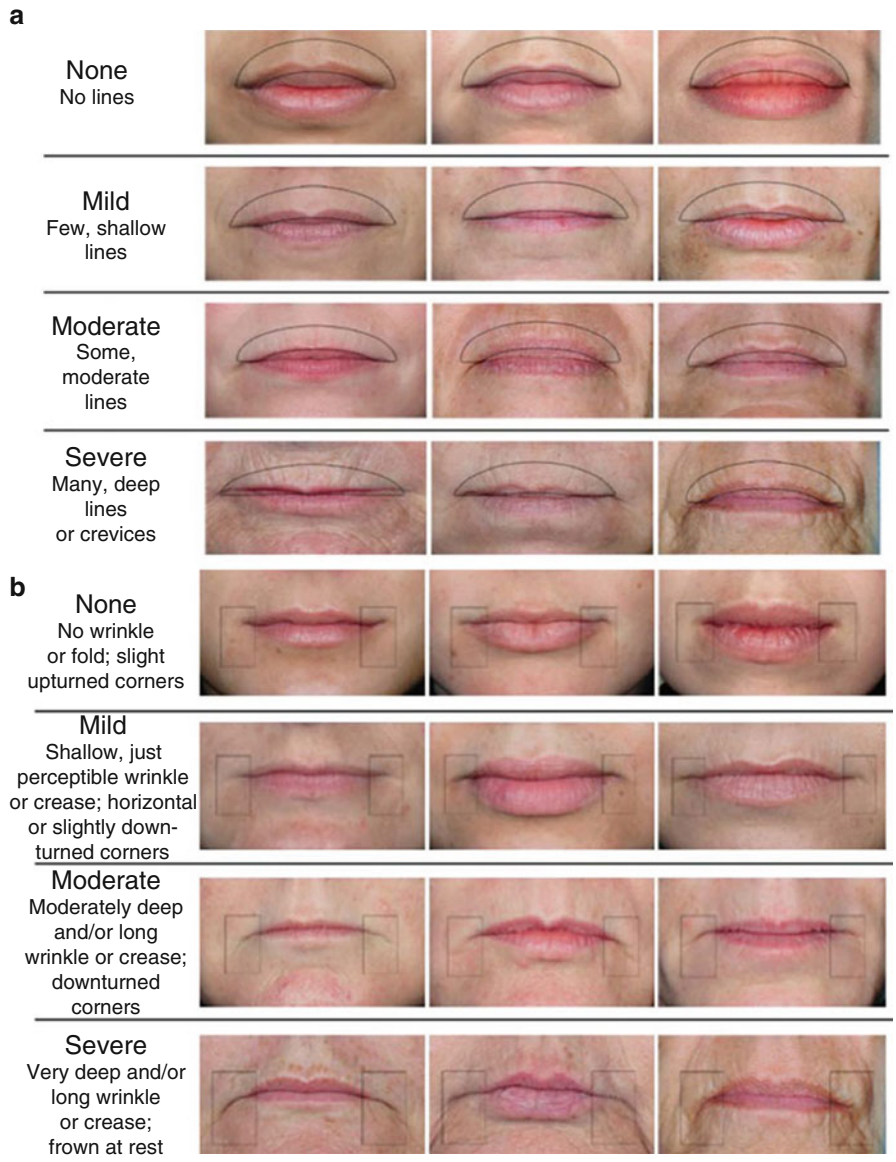


Fig. 6 Photographic scales for the classification of perioral aesthetic features by Cohen. Supralabial lines (**a**); Corners of the lips (**b**)

there are three two-dimensional photographic scales to evaluate perioral lines at rest (Cohen et al. 2014) (Fig. 6). The number of existing scales for assessing wrinkles makes it difficult to compare the efficacy of cosmetic techniques in the treatment of photoaged skin. For this reason, there is a need to adopt a single, standardized, objective, and reliable method for the assessment of facial wrinkles and furrows.

Take-Home Messages

- Beauty needs to be assessed holistically. This means looking beyond the intuitive perception of beauty to only derive from the attraction of our facial beauty but also take other body parts such as our neck and hair into account.

- Changes in the structures of the skin, muscle action, fat compartments, and bone remodeling are described on the facial aging process.
- The face evaluation is divided into three thirds (upper, middle, and lower) to identify its symmetry and balance.
- The aging facial shape changes and is called facial squaring that identifies when an inverted trapezoid tends to become square-shaped over the years.
- From an aesthetic point of view, it is vital to identify the classification of aging of each person for an anatomical treatment.
- The aging classification is measured in scales by Glogau photoaging, numerical photography grading scale by Carruthers front, and nasolabial and perioral scale to develop an objective assessment of what beauty is.

Cross-References

- ▶ Anamnesis and Physical Evaluation
- ▶ Approach in Photodamaged Skin, Melasma, Acne, and Rosacea
- ▶ Skin Anatomy, Histology, and Physiology

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Assessment of Skin Photoaging with Reflectance Confocal Microscopy

Patrícia M. B. G. Maia Campos, Maísa Oliveira de Melo, and Daiane Garcia Mercurio

Abstract

The reflectance confocal microscopy is a very important and widely used technique to evaluate the morphological and structural characteristics of the skin, including the photoaging effects on the epidermis and dermal-epidermal junction. The analyses are made with the equipment VivaScope 1500®, which utilizes a laser beam of 35 mW, in a near-infrared wavelength (830 nm) and 30× objective lens. With this new technique, it is possible to scan even the least accessible body parts with no discomfort to the patient, offering the possibility to assess the effect of antiaging treatments and to identify early signs of solar damage. It is utilized in dermatological trials, in specific skin lesions, and the progress during a treatment can also be analyzed. In the cosmetic area, among other objectives, this technique is widely used in the assessment of skin aging and the efficacy of cosmetic products in real conditions of use. The main characteristics that can be studied in this analysis are the epidermal thickness, dermal papillae depth, skin pigmentation, and kerotinocyte morphology. In addition, reflectance confocal microscopy (RCM) is a reliable diagnostic technique for evaluation of skin photoaging with objective criteria. In summary, the RCM is a very important technique to analyze the skin morphology without invasive measures, allowing conclusive and complementary results, creating substantial skin biology knowledge.

Keywords

Reflectance confocal microscopy • Skin photoaging • Imaging techniques • Skin pigmentation • Skin morphology and structure • Clinical trials • Dermocosmetic products

Contents

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Introduction

The aged skin presents distinct morphological and structural characteristics, with disorganized keratinocytes, that are a result of lower cell renewal in this skin type.

New innovative imaging techniques have been recently developed in the dermatological area, allowing a real-time and noninvasive visualization of the skin layer morphology and specific conditions. Furthermore, the cosmetic industry has been investing in the development of cosmetic formulations containing active ingredients that may act in skin protection in order to delay the photoaging process, and the previously mentioned techniques may also assist in the clinical efficacy of proposed claims.

In this context, reflectance confocal microscopy (RCM) highlights as a noninvasive skin imaging technique based on the imaging of light reflected by the living tissue. It has been widely used in the dermatological practice, especially in the diagnosis of skin diseases and evaluation of cutaneous characteristics, as it provides a cellular visualization in a quasi-histological resolution of the cell and tissue characteristics in real time. Cellular alterations in the epidermis, cellular renovation, epidermal hydration, dermal-epidermal junction pattern, and structural properties of upper dermis are also possible to be analyzed with this technique, which is highlighted as a powerful method to evaluate the morphological and structural properties of photodamaged skin.

The images obtained by the confocal microscope enable the evaluation of cutaneous characteristics, such as the thickness of the different layers of the epidermis, the organization of keratinocytes, the changes in the pigmentation pattern, the number of dermal papillae per area, the shape of the dermal papillae's contours, the size of sebaceous glands, the structure of the collagen network, the count and size of pores and microcomedones, and the evaluation of primary signs of cutaneous irritation. Many studies describe RCM as a proper and reliable technique for the description and quantification of structural characteristics of the epidermis and upper dermis, overcoming the disadvantages of the invasive histological evaluation. Due to the highly diverse possibility of technical applications, the elucidation and interpretation of RCM images related to skin aging provide subsidies for its application in the dermatology clinic, especially in evaluating skin alterations resulting from the aging process (Mercurio and Maia Campos 2015).

The application of RCM allows the identification of changes in the epidermis, cell morphology, and extracellular matrix (collagen) at the level of the epidermis, dermoepidermal junction, and papillary dermis, respectively. Changes in these parameters are correlated with chronological aging and are aggravated with solar exposure, leading to a loss of small skin furrows, which results in wider and less intersecting furrows, an irregular epidermal honeycomb pattern, mottled pigmented keratinocytes/melanocytes, irregularity of the papillary rings, and loss of thin collagen fibers and presence of collagen clods (Andrade et al. 2015).

In this context, the RCM is presented as an innovative noninvasive skin imaging technique to morphological and structural skin characterization in real-time conditions.

Basic Concepts

The reflectance confocal microscopy is a very important and widely used technique to evaluate the morphological and structural characteristics of the skin, including the photoaging effects in the epidermis, dermal-epidermal junction, and dermis.

The confocal images are formed/obtained based on the emission of light that illuminates a small area within the tissue. The light is reflected and passes through a small opening in the microscopy, and with that, the image is created on the detector. This small opening does not allow the reflected light from another point of the tissue to reach the detector; this way, only the light reflected from the region in focus is detected. Thus, to create the image of the entire interest area, each point of the skin surface has to be

recorded (Mercurio and Maia Campos 2015; Andrade et al. 2015).

The presence of different skin microstructures leads to natural variations in the refractive index, which provides contrast in the image. For example, the cytoplasm has a refractive index similar to water (1.33) and is represented with a very low contrast. On the other hand, melanin has relatively high refractive index (1.7), working as a natural contrasting agent. Other skin components that provide contrast are keratin, mitochondria and other cytoplasmic organelles, chromatin present in the nuclei, and the dermal collagen (Bielfeldt et al. 2011; Majdzadeh et al. 2015).

The equipment VivaScope 1500® (Caliber Imaging & Diagnostics, Inc., USA) utilizes a laser beam of 35 mW, in a near-infrared wavelength (830 nm) and 30× objective lens. It can reach a depth of 200–300 mm with 0.5–1 mm in the lateral resolution and resolution axial of 2–5 mm. Each obtained image has a visual field of 500 × 500 uM (Mercurio and Maia Campos 2015).

With these differences in the refractive index, it is possible to identify the different skin layers by their specific morphological characteristics. The first layer, stratum corneum, is the top layer of the skin and presents a high brightness due to the light backscatter and content of keratin. The second layer is the stratum granulosum, where it is possible to observe the granular cells that are larger, with a bright cytoplasm and dark nuclei. These cells have the tendency of forming a typical "honeycomb" pattern when in good conditions, and this pattern is an important parameter to be considered in skin aging studies. Below that, it is possible to observe the stratum spinosum, which also forms a "honeycomb" patter, but with smaller and thinner keratinocytes.

In the basal layer, right above the dermal-epidermal junction, is it possible to observe bright refractive cells, usually containing melanin. In the dermal-epidermal junction, the dermal papillae are visible, which are another skin aging parameter, as their thickness is usually smaller in mature skins. In this layer, the basal cells form rings around the sectioned dermal papillae.

In the papillary dermis, below the dermal-epidermal junction, the collagen and elastin fibers create a highly refractive structure, and in the reticular dermis, these fibers appear larger and denser.

History

In 1967, the confocal microscopy was introduced as a new technology in the dermatology field. It is a technique based on the increase of contrast in the microscopic image and construction of three-dimensional images through the use of an opening hole, called pinhole, which allows a high image definition in samples that are thicker than the focal plane. At this time, this new technology enabled the visualization of cells in uncut and unstained ex vivo tissue (Pierard 1993).

This milestone represents a significant advance in science, and it was widely applied on the evaluation of thick semiopaque tissues. In 1991, Jester et al. reported the in vivo confocal microscopy, to be used to analyze different in vivo tissues in real time, such as the brain, eye, and tooth, among others. This innovation allowed the evaluation of the dynamic events of the human body, showing that the histological information obtained by in vivo methods were very similar to the histological results of the ex vivo tissue. Moreover, the benefit of evaluating changes over time in the same place and tissue was unquestionable; this technology was considered then a "new paradigm in microscopy" (Jester et al. 1991; Corcuff et al. 1993).

Before the great application potential, new skin assessments by this technique have been developed, and several studies have been conducted comparing with conventional histology, considering the physiological and pathological skin conditions. The melanin was evidenced as a contrast agent by Rajadhyaksha et al. (1995), with the evaluation of different skin phototypes (Rajadhyaksha et al. 1995).

In 1997, the American company Lucid introduced the VivaScope® equipment, with a laser source of 830 nm with a power of 30 mW that does not cause any damage to the tissue. In 2000,

the VivaScope 1500® was released, and in 2006, the portable VivaScope 3000® was introduced to the market.

The layers observed by RCM are well described, and knowledge of the morphology of healthy skin is very important for the detection of skin disorders (Mercurio and Maia Campos 2015). The images obtained by confocal microscopy enable the evaluation of skin features, such as the thickness of the different layers of the epidermis, identification of hyperkeratotic areas in the superficial epidermis, and visualization of sunburned cells, surface appearance of the skin, keratinocyte organization, changes in pigmentation pattern, amount of dermal papillae by area, shape of the dermal papillae, size of the sebaceous glands, structure of the collagen network, count and size of pores and microcomedones, and acne characteristics (Kawasaki et al. 2015; Manfredini et al. 2015; Sauermann et al. 2002; Ulrich et al. 2009; Wurm and Soyer 2012; Xiang et al. 2016). Moreover, the technique has been used for the evaluation of primary signs of irritation (Swindells et al. 2004) and skin penetration studies (Alvarez-Román et al. 2004).

The laser reflectance confocal microscopy has been extensively applied in the dermatological clinic and is a revolution in the diagnosis of skin diseases and evaluation of skin characteristics, allowing cell visualization in an almost histological resolution, presenting the cell and tissue characteristics by a noninvasive method in real time (Branzan et al. 2007; Gonzalez and Gilaberte-Calzada 2008).

Classifications

The skin aging process can be divided into two categories, the chronological aging that is an internal response of the human organism and the extrinsic skin aging that is caused by external environmental factors, such as pollution, smoking, and especially solar radiation, and it can affect people who still have skin that is considered young. This way, with the use of RCM, several changes in different skin layers can be analyzed in the photoaged skin.

- **Epidermis**: Stratum corneum. The mature or aged skin presents a greater thickness of the stratum corneum and size of corneocytes. Hyperkeratosis is a characteristic of the photoaged skin, in which a defective stratum corneum, composed of corneocytes poorly organized with varying sizes and shapes, is produced (Huzaira et al. 2001; Kligman and Kligman 1986). The reduction in cell renewal, which is also a characteristic of aging, can contribute to the thickening of the stratum corneum as well as to increase the size of the corneocytes.

  In a healthy/young skin, the viable epidermis is presented in a "honeycomb" pattern. During the aging process, this pattern suffers a size and shape polymorphism in keratinocytes, losing its "honeycomb" characteristic and gaining irregular pigmentations due to an accumulation of melanin in the keratinocytes (Fig. 1).

  This characteristic morphological profile reflects the uneven, defective, and damaged response of the keratinocyte and melanocyte functionality against the aging and chronic exposure to UV radiation (Andrade et al. 2015; Nishimori et al. 2001; Longo et al. 2013b).

- **Dermal-epidermal Junction**: The dermal-epidermal junction's pattern is completely altered in the aged skin. The main alteration is observed on the flattening or complete loss of the dermal papillae, which is correlated with a thinner epidermis (Fig. 2).

- **Dermis**: The characteristics of the papillary dermis have been well described in the literature, allowing the study of the morphological dermal in studies. However, the evaluation of the RCM in the dermis has some limitations, since below the basal layer a reduction in the

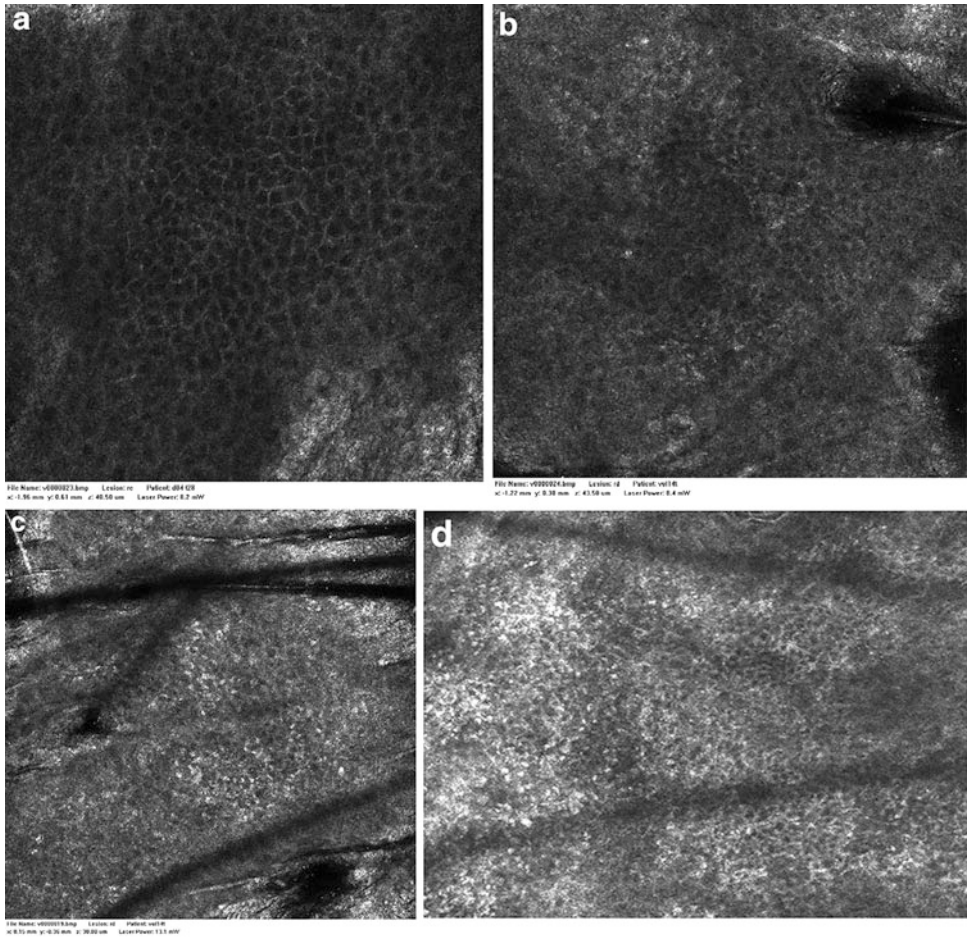

Fig. 1 RCM images of epidermal morphological and structural properties of skin. (**a**) Non-damaged viable epidermis: homogenous size and shape of keratinocytes (*young skin*). (**b**) Viable epidermis with irregularity of the epidermal honeycomb pattern. (**c**) Pigmented epidermis with pigmented keratinocytes. (**d**) Viable epidermis with irregularity of the epidermal honeycomb pattern and pigmented keratinocytes (*mature skin*)

technique resolution can be observed. Papillary dermis has fine and highly refractive collagen fibers in young skin. On the other hand, in the aged skin, the fibers are barely visible and have a huddled appearance. The aged collagen undergoes progressive changes of fine fibers, coarse fibers, or amorphous content hyporefractive (Nishimori et al. 2001). In some cases, it is possible to observe the presence of solar elastosis in the aged skin (Fig. 3).

In the papillary dermis, the young skin presents thin and highly refringent collagen fibers, whereas in aged skin, the fibers are hardly visible and have a shrunken and amorphous appearance. In some cases, it is possible to observe the presence of solar elastosis in the aged skin. Based on the confocal microscopy analysis, it was possible to observe an uneven pigmentation pattern, keratinocytes unevenly distributed, flattening of the dermoepidermal junction, presence of deteriorated collagen fibers, and severe solar elastosis in the aged skin.

The images displayed by RCM are in accordance with the histological findings that are

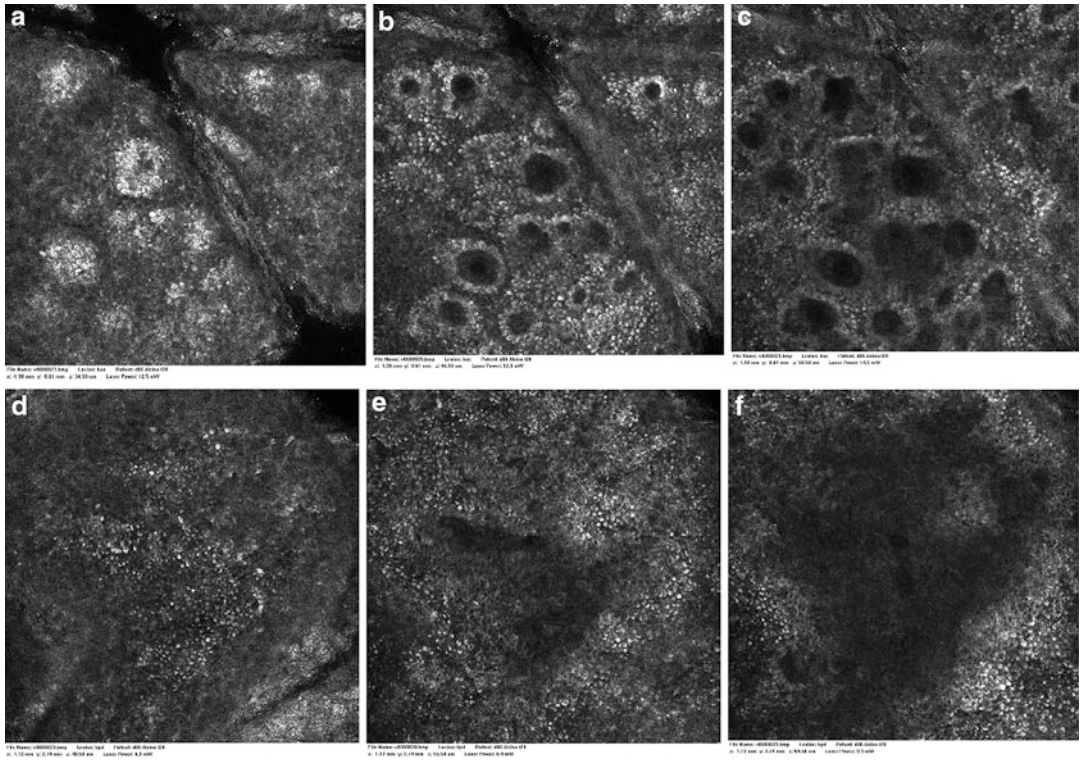

Fig. 2 Dermal-epidermal junction pattern of young (**a**–**c**) and aged skin (**d**–**f**). Effacement of rete ridges and flattening of dermal-epidermal junction is observed in photodamaged skin (scale, 500 × 500 μm)

well known, in which the photoaged dermis has a substitution of the normal fibrillar pattern of large amounts of degraded elastic fibers, thick, tangled, and nonfunctional (Mizukoshi et al. 2015; Wurm and Soyer 2012; Bilac et al. 2014a; Kligman and Kligman 1986b), besides having disruption and fragmentation of collagen (Mercurio et al. 2016).

Pigmentation Disorders: Epidermal Mottled Pigmentation, Solar Lentigos

The VivaScope® is also a very useful technique to analyze pigmentation disorders, as melanin is the main endogenous source of reflectance on RCM analysis, playing a very important role on the image contrast.

This way, this technique allows the noninvasive longitudinal quantification of epidermal pigmentation in the skin, preserving the integrity of the tissue, with the advantage of being easily reproduced over time and on the same location. With this, it is possible to follow the development of specific skin damages in a cellular level, which is very useful during dermatological treatments (Gianeti et al. 2012). Different types of pigmentation disorders exist and are possible to be observed on RCM (Figs. 4, and 5)

Lentigines are small, sharply circumscribed, pigmented macules surrounded by skin which is normal in appearance. Hyperplasia of the epidermis and increased pigmentation of the basal layer are evident upon histology. Langley et al. evaluated 10 patients using confocal microscopy, including six cases of lentigines and four lentigo maligna (Diridollou et al. 2001). The highlight feature in the lentigines condition is the increased density of dermal papillae surrounded by bright monomorphic layers of cells. Dermal papillae that are usually in an annular, polycyclic shapes or

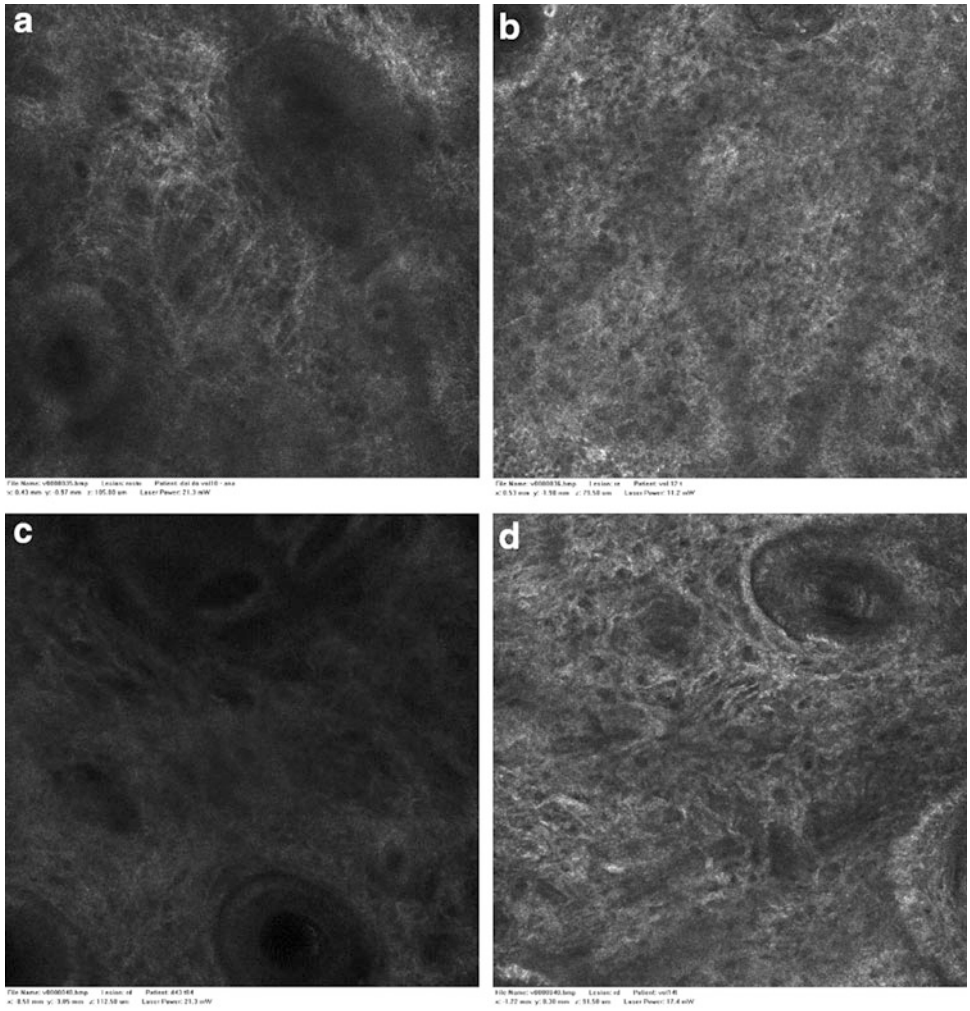

Fig. 3 RCM images of dermis of sun-exposed area (*face*). (**a**) Young dermis with thin collagen fibers. (**b**) Damaged dermis with loss of thin collagen fibers and presence of coarse collagen. (**c**) Damaged dermis with hyporefractive and huddled collagen. (**d**) Curled fibers representing solar elastosis (scale, 500 × 500 μm)

formed papillary projections are surrounded by single cell layers of bright monomorphic cells.

Melanophages can be seen inside the dermal papilla. Solar lentigo, on the other hand, is characterized as a unique cerebriform appearance of the basal cell layer, presumably because of complex anastomosing of rete ridges (Lagarrigue et al. 2012; Gonzalez and Gilaberte-Calzada 2008b).

Different Skin Alterations: Actinic Keratosis

In cases of actinic keratosis, which is one of the most common precancerous lesions of the skin that usually affect aged skin that suffered excessive exposure to ultraviolet light, an irregular hyperkeratosis in the stratum corneum is possible to observe in a RCM analysis. The stratum granulosum is very similar to one in a healthy skin, which contains keratinocytes with dark nuclei and bright cytoplasm. The difference is observed in the shape and size of these cells, as an epidermal nuclear enlargement and pleomorphism is visible, along with architectural disarray on the lower portion of the epidermis (Calzavara-Pinton et al. 2008; Langley et al. 2006).

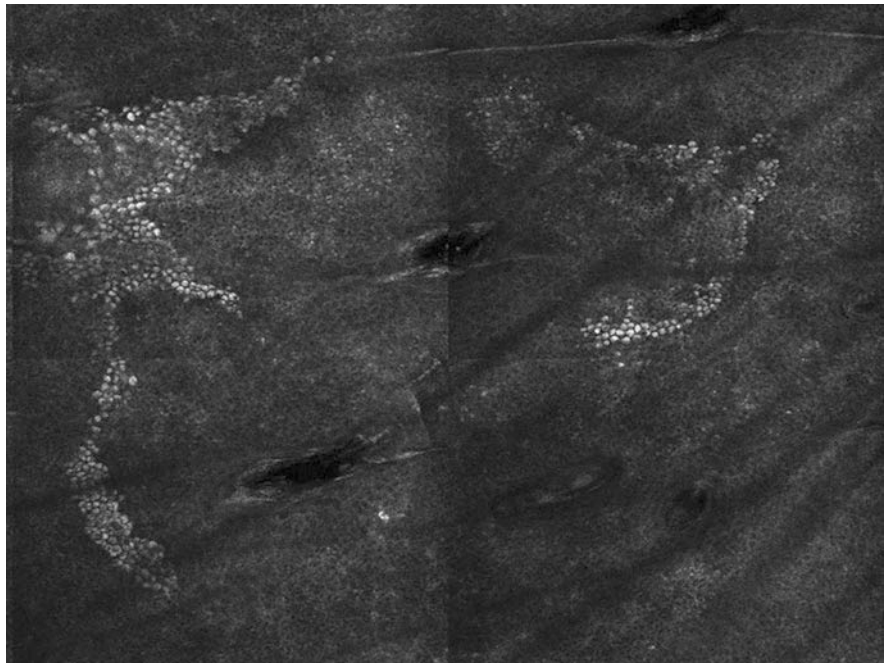

Fig. 4 RCM image of irregularly distributed (mottled) pigmented keratinocytes/melanocytes. Scale 1 mm × 1 mm

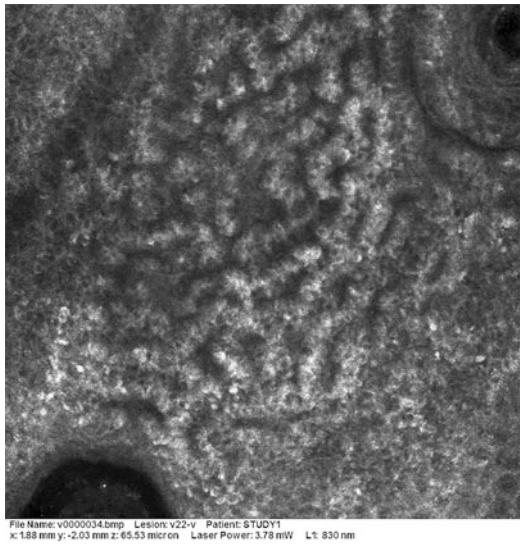

Fig. 5: RCM image of a solar lentigo

The risk of progression of a single actinic keratosis to a full-thickness squamous cell carcinoma is still to be quantified, but it has been estimated at approximately 10%. Irregular hyperkeratosis in the stratum corneum and broad, uniform, and regularly spaced keratinocytes in the stratum spinosum/granulosum with evident dark nuclei, which are sometimes larger and more irregular than in the normal skin, were the characteristic signs of actinic keratoses (Aghassi 2000).

Conclusion

Considering the importance of the skin pigmentation pattern and knowledge in the photoaging process, the application of RCM is an innovative strategy to identify the changes on the skin at cellular level.

This way, the RCM is a very important technique to analyze the skin without invasive measures, allowing the identification of changes in architecture, cell morphology, and extracellular matrix (collagen) at the level of the epidermis, dermoepidermal junction, and papillary dermis, which result in conclusive and complementary results, creating substantial skin biology knowledge.

Take-Home Messages

- The reflectance confocal microscopy is a very important technique to analyze the skin morphology without invasive measures.
- The reflectance confocal microscopy can be considered a reproducible and robust technique for assessing the thickness of the skin layers in long-term clinical trials.
- Reflectance confocal microscopy is a reliable diagnostic technique for evaluation of skin photoaging with objective criteria.
- RCM offers conclusive and complementary results, creating substantial skin biology knowledge.

Cross-References

- ▶ Approach in Photodamaged Skin, Melasma, Acne, and Rosacea
- ▶ Skin Anatomy, Histology, and Physiology

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Approach in Photodamaged Skin, Melasma, Acne, and Rosacea

Sandra Maria Barbosa Durães, Rosa Rabello Fonseca, and Maria Claudia Almeida Issa

Abstract

Acne, rosacea, melasma, and photodamaged skin are the cutaneous diseases that most commonly lead to imperfections, which often decrease the quality of life and cause low self-esteem. In each of the four conditions, a clinical classification of gravity guides a rational treatment for best results with minimal adverse effects. This chapter covers the basic clinical directions, adding new pathophysiological knowledge, that modified the old concepts and are used as basis for new approaches. Topical and systemic agents are reviewed in detail, as well as new agents recently incorporated into the therapeutic arsenal.

Keywords

Acne • Rosacea • Melanosis • Skin aging • Diagnosis • Treatment

Contents

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Photodamaged Skin

Introduction

Photoaging is characterized by a complex process of skin changes induced by ultraviolet light exposure. It results in premature aging of the skin and is superimposed on the changes caused by chronologic aging. Not all photoaging is equal. The process is influenced by skin type and ethnicity. The degree of photoaging also depends on geographic location (i.e., latitude and altitude), extent of sun exposure in relation to occupation and lifestyle, and photoprotective practices, including using sunscreens and photoprotective clothing, and seeking shade. Generally, people are concerned about appearance and are influenced by society, culture, and personal values. Aesthetic ideals of beauty vary, yet the appearance of youthfulness remains a constant benchmark. More often people go to dermatology offices following looking better and stop or at least slow the aging process. Photoaging plays an important role in the degree to which youthfulness is retained despite advancing age (Davis and Callender 2011). Improved understanding of the skin's innate UV protective mechanisms has also given rise to several novel treatment concepts that promise to revolutionize this field within the coming decade. Such advances should not only allow for the improved appearance of skin in middle age and beyond but also greatly reduce the accompanying burden of skin cancer (Yaar and Gilchrest 2007).

Epidemiology

Photoaging is more prevalent among populations with fair skin. Fitzpatrick skin types I, II, and III are more prone to photoaging than skin types IV. In populations with darker skin, wrinkling is not readily apparent until the age of 50 and the severity is not as marked as in fairer skinned populations of similar age (Goh 1990). One study found that the onset of wrinkles in Chinese women occurred on average 10 years later than in French women (Nouveau-Richard et al. 2005).

Photoaging is directly associated with cumulative sun exposure and, by extension, increasing age. Other factors include geographic location, such as high altitude and proximity to the equator where the harmful effects of ultraviolet light from the sun are most severe. Lifestyle practices, including outdoor occupations and outdoor recreational activities, increase cumulative sun exposure. For example, farmers, sailors, construction workers, and truck drivers frequently show severe effects of sun exposure over a lifetime. Indoor tanning is a practice that is also responsible for accelerated photoaging (Urbach et al. 1976).

Factors that diminish the features of photoaging include rigorous sun-protection practices such as daily use of sun protection, clothes, and hats with FPS beyond avoidance sun exposition in periods of higher incidence of UV radiation such as 10 am to 16 pm.

Pathogenesis

Photoaging is thought to occur through the generation of reactive oxygen species (ROS), activation of signaling mechanisms resulting in the induction of matrix metalloproteinases (MMPs), decreased synthesis of collagen, and inflammation. Despite the repair process that follows, including tissue inhibitors of MMPs, these disorganized collagen fiber result in invisible solar scars, causing the characteristic wrinkling of photoaged skins (Varani et al. 2006; Widgerow and Grekin 2011).

Both UVA (320–400 nm) and UVB (290–320 nm) seem to be implicated in the photoaging process, although UVA is emerging as the major contributor because it penetrates deeper into the dermis and reaches the earth at least 10-fold more abundantly than UVB. UVB radiation is mainly absorbed in the epidermis by

cellular DNA, inducing damage with formation of cyclobutane pyrimidine dimers. UVB is responsible for sunburn, photocarcinogenesis, and immunosuppression (Benjamin et al. 2008).

Cumulative UVA radiation causes damage to the dermal extracellular matrix and blood vessels. UVA also indirectly damages DNA, as well as lipids and proteins, through the generation of reactive oxygen species (ROS). ROS cause oxidative damage to cellular components such as cell membranes, mitochondria, and DNA. Mitochondria are the main endogenous source of ROS and are produced during the conversion of ADP to ATP.

Endogenous ROS, including superoxide anion, hydrogen peroxide, and singlet oxygen, activate cytokine and growth factor receptors, which in turn induce transcription factor activator protein 1 (AP-1) and NF-kB (Han et al. 2014).

Figure 1 demonstrates the pathogenesis of photoaging: UV radiation activates growth factor and cytokine receptors, which induce transcription factor AP-1. The induction of AP-1 promotes collagen breakdown by upregulating matrix metalloproteinases (MMP), including interstitial collagenase (MMP-1), stromelysin-1 (MMP-3), and 92 kDa gelatinase (MMP-9) (Fisher et al. 2002). The combined actions of MMP-1, MMP-3, and MMP-9 degrade most of type I and III dermal collagen (Sternlicht and Werb 2001). Furthermore, AP-1 inhibits collagen production by decreasing gene expression of types I and III procollagen in the dermis. AP-1 binds to the transcriptional complex responsible for procollagen transcription or blocks the activity of transforming growth factor beta (TGF-b), a cytokine that promotes procollagen formation. With repeated sun exposure, degraded collagen accumulates over time and attenuation of collagen production results in the clinical and histologic features of photoaging (Fisher and Voorhees 1998). The activation of NF-kB by ROS regulates the expression of proinflammatory cytokines, such as interleukin (IL)-1b, TNF-a, IL-6, IL-8, and various adhesion molecules. These cytokines, in turn, can amplify AP 1 and NF-kB pathways, further enhancing the response to UV radiation (Yamamoto and Gaynor 2001; Senftleben and Karin 2002).

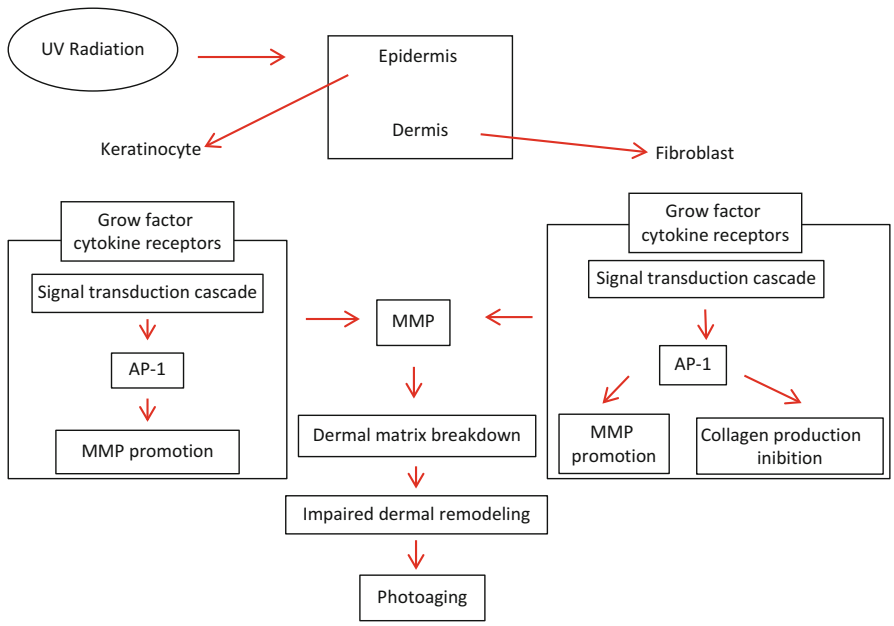

Fig. 1 Pathogenesis of photoaging. AP-1 (transcription factor activator protein 1), MMP (matrix metalloproteinases). Based on Fisher GJ, Kang S, Varani J, et al. Mechanisms of photoaging and chronologic skin aging. Arch Dermatol 2002;138:1462

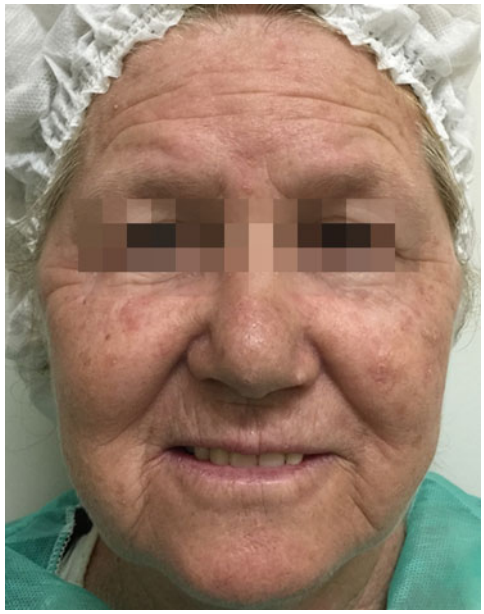

Fig. 2 Photodamaged skin with actinic keratosis

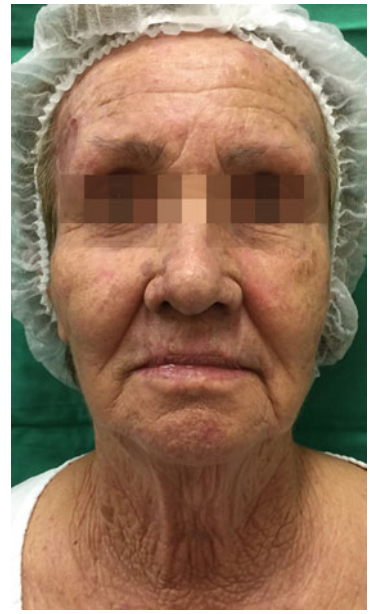

Fig. 3 Photodamaged skin: frontal and glabellar wrinkles, nasolabial fold, and laxity of the face and neck

Clinical and Histological Changes of Photodamaged skin

Photoaging can manifest as rhytids, lentigines, telangiectasias, mottled pigmentation, coarse texture, loss of translucency, sallow color, laxity, and decreased elasticity and turgor (Fig. 2). More severe photoaging may result in accentuated ridging, deep furrows, leathery appearance, severe atrophy, open comedones, milia, cobblestone effect from elastosis, actinic purpura, and epidermal and dermal thickening (Figs. 3 and 4) (Shirakabe et al. 2003). Chronologic aging is dominated by fine lines and increased skin laxity. The latter is primarily due to soft tissue volume loss from fat atrophy, gravity-induced soft tissue redistribution, and reduction of facial skeletal support related to bone resorption (Gordon and Brieva 2012).

Sun-induced cutaneous changes vary considerably among individuals, undoubtedly reflecting inherent differences in vulnerability and repair capacity for the solar insult. Even among white Caucasians the gross appearance of photodamaged skin of individuals with skin types I and II often differs from that of individuals with skin types III and IV (Yaar and Gilchrest 2007).

Darker skin is more photoprotected than fair skin because of the increased melanin content. Thus, individuals with higher Fitzpatrick skin types are inherently more protected because they generally experience the effects of photoaging 10–20 years later and with less severity (Han et al. 2014).

Ethnicity plays a strong factor in determining the specific clinical features of photoaging. Wrinkle patterns and pigmentary changes differ between white and Asian skin (Shirakabe et al. 2003). Aryan origin shows deeper wrinkles, particularly around the eye area and forehead, even though they had darker skin on average than Mongolian origin. Thus, ethnic origin and genetics are independent factors in determining the effects of photoaging. An epidemiologic study investigating the role of genetics compared Japanese women from Japan and white women from Germany. The Japanese women had less facial wrinkling and more pigment spots than their German counterparts (Fig. 5). Plausible explanations for the underlying differences include higher antioxidant levels in fasting blood

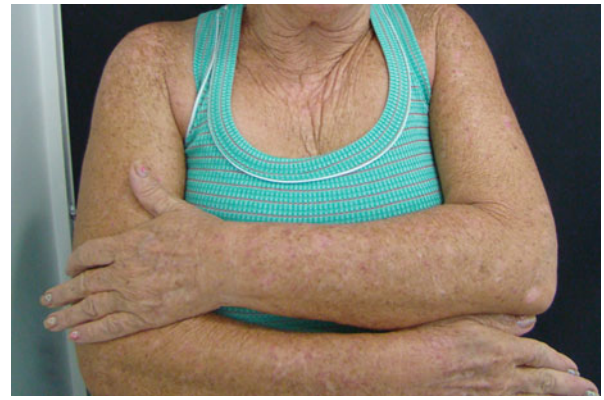

Fig. 4 Photodamaged skin (body): melanosis, laxity, wrinkles, and actinic keratosis

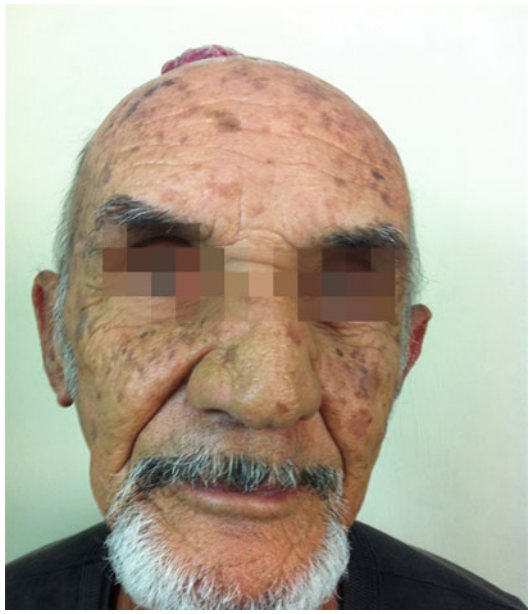

Fig. 5 Photodamaged skin with skin cancer on the head

(for less wrinkling) and greater frequency of the SLC45A2 gene allele involved in melanin synthesis (for more pigmented lesions) in Japanese women (Vierkotter and Krutmann 2012).

Microscopic changes in photodamaged skin affect the epidermis and dermis. In photoaging, epidermal changes include either atrophy with thinning of the spinous layer and flattening of the dermoepidermal junction (loss of rete ridges) or epidermal thickening and acanthosis (Kurban and Bhawan 1990).

Histologically, the dermis displays tangled masses of degraded elastic fibers as well as an amorphous mass composed of disorganized tropoelastin and fibrillin. In addition, the amount of ground substance, largely composed of glycosaminoglycans and proteoglycans, increases in photodamaged skin, whereas the amount of collagen decreases. Also, photodamaged skin frequently displays an increased number of hyperplastic fibroblasts as well as increased inflammatory cells, including mast cells, histiocytes, and other mononuclear cells, giving rise to the term heliodermatitis (literally, "cutaneous inflammation due to sun"). Dermal vasculature in mildly photodamaged skin displays venule wall thickening; in severely photodamaged skin thin vessel walls with compromised perivascular veil cells display dilations – telangiectases (Yaar and Gilchrest 2007).

Treatment

Photoprotection

The first line of defense against photoaging is photoprotection, including seeking shade when outdoors and using sunscreens and protective clothing. Topically applied sunscreens protect by absorbing or reflecting radiation at the skin surface. UV filters can be grouped into two broad categories: organic (previously called chemical) and inorganic (previously called physical) (Han et al. 2014).

Over the past two decades, sunscreen technology has made enormous strides to achieve superior UV protection and provide an improved sensory profile. Whereas early sunscreens

provided low UVB protection and virtually no UVA protection, modern sunscreens now incorporate novel UV filters, UV boosters, and photostabilizers that provide considerable protection against both UVA (320–400 nm) and UVB (290–320 nm) radiation. In terms of UV protection, the major area of progress has been the extension of coverage to the long UVA-I (340–400 nm) range. Among the 17 UV filters currently approved by the FDA, only two of these filters, avobenzone and zinc oxide (ZnO), can absorb long UVA-I radiation. Avobenzone is inherently photo unstable, with an activity level that degrades by 50% after 1 hour of UV exposure. Furthermore, when avobenzone is combined with octinoxate, a common UVB filter, the degradation of both compounds is accelerated.

Aside from new filters and photostabilizers, the vehicle compounds into which modern sunscreens are formulated have also boosted the UV protective properties of these products. This is because ingredients comprising the vehicle have decidedly synergistic effects on the degree of UV protection provided by the UV filters in the final formulation. In fact, the vehicle is equally if not more important than the type and concentrations of the UV filters utilized. This is because vehicles that dissolve and disperse UV filters in a uniformed fashion can enhance overall UV protection. Technical advancements that have improved the visual and sensory profiles of sunscreen are also of important note. Sunscreens incorporating the macro-sized inorganic filters TiO2 and ZnO have long been utilized by the sunscreen manufacturing industry. However, TiO2 and ZnO molecules of a sufficient size frequently extend into visible light range when applied, leaving an unacceptable opaque white appearance on the skin. Because these products are not cosmetically elegant, sunscreens containing inorganic filters were not widely accepted until recently. To overcome this visual drawback, modern sunscreens now use of modern sunscreen products, technical breakthroughs have also improved their sensory profiles.

Consumers often complain that most sunscreen products on the market are too greasy and oily. For example, octocrylene, a UVB filter also used as a photostabilizer for avobenzone, has an extremely oily texture. Compounding the texture issue is the need for sunscreens designed for aquatic, sport, and outdoor activities to be water and sweat resistant. Although water-resistant polymers have been designed, which hold the sunscreen formulation onto the skin surface, these ingredients can leave a tacky or sticky feel to the product. To improve the tactile and sensory profiles of sunscreen products, silicones, silicas, and other slipping agents are added to reduce the unpleasant and sticky feeling. The addition of polymeric surfactants, such as acrylate cross polymers, can also provide rapid emulsion-breaking characteristics that allow to the product to spread easily on the skin and improve the overall textural profile after drying (Burnett et al. 2012).

The protective benefit derived from combining AOxs with sunscreen has been demonstrated in human studies (Matsui et al. 2009). Despite the potential benefit, formulating products that combine AOxs with sunscreen is a challenge. To ensure the efficacy of AOxs in the final products, a number of technical requirements must be fulfilled (Chen et al. 2012).

Recent studies show that orally administered *Polypodium leucotomos* has antioxidant and photoprotective properties. *Polypodium leucotomos* is a tropical fern that is native to Central and South America. Clinical and nonclinical research performed over the past 30 years has demonstrated that extracts of *P. leucotomos* possess beneficial properties attributed to the presence of numerous compounds with antioxidant and photoprotective properties including p-coumaric, ferulic, caffeic, vanillic, 3,4-dihydroxybenzoic, 4-hydroxybenzoic, 4-hydroxycinnamic, 4-hydroxycinnamoyl-quinic, and chlorogenic acids. When taken orally, *P. leucotomos* provides some degree of protection against the harmful effects of ultraviolet radiation, thereby helping to minimize the photoaging effects of sunlight, including hyperpigmentation and textural changes. *P. leucotomos* may owe its ability to help in preventing the photoaging process specifically by maintaining the structural integrity of the extracellular matrix that typically is affected by UV damage through increased

matrix metalloproteinase expression and inhibition of collagen synthesis (Nestor et al. 2014).

Retinoids

The ability of topical retinoic acid, also termed tretinoin, to improve photoaging changes in skin was suggested by the observation of middle-aged women under treatment with the drug for acne, supported by studies in the hairless mouse model (Kligman et al. 1984; Kligman et al. 1986) and later definitively demonstrated in patients (Weiss et al. 1988).

Topical retinoids are the mainstay of treatment of patients with mild to moderate photoaging. Retinoids are a class of naturally occurring or synthetic compounds related to vitamin A, also known as retinol. Retinol is naturally converted in the body to its most biologically active form, retinoic acid, as well as to its other derivatives, retinaldehyde and retinyl ester. Various natural and synthetic retinoids increase collagen production, induce epidermal hyperplasia, and decrease keratinocyte and melanocyte atypia (Griffiths et al. 1993b; Fisher et al. 1996; Cho et al. 2005). Clinically, they reduce the appearance of fine lines, improve skin texture, correct tone and elasticity, and slow the progression of photoaging (Han et al. 2014). Tretinoin, or all-trans-retinoic acid, is the most widely investigated photoaging therapy. Tretinoin 0.05% and tazarotene 0.1% are the only two retinoids approved by the US Food and Drug Administration (FDA) for this indication. Other topical retinoids for photoaging include adapalene, a synthetic derivative available by prescription, and retinol, which is found in many antiaging cosmeceutical products (Kang et al. 1995). Topical retinoids may cause irritant reactions, such as scaling, redness, burning, and dermatitis, limiting patient compliance. Retinoids should be initiated at the lowest effective dose to minimize adverse effects.

The use of systemic retinoids aiming to reverse skin damage provoked by sun exposure has been receiving special attention in the past years. Oral isotretinoin has been prescribed in low doses for the treatment of cutaneous photoaging by some healthcare professionals with satisfactory clinical results. Scientific evidences supported by histopathological and morphometric studies showed that low dosages of oral isotretinoin, 10 and 20 mg thrice a week, seem to be an effective therapeutic option for photodamaged skin. However, it is important to evaluate the costs and benefits for this indication (Rabello-Fonseca et al. 2009).

Cosmeceuticals

Cosmeceuticals encompass a heterogeneous category of nonprescription topical products, including antioxidants, vitamins, hydroxy acids, and plant extracts. Cosmeceuticals are marketed to the consumer based on claims of their antiaging effects. They are touted to lighten and brighten, reduce wrinkles, correct blemishes, and lead to overall skin rejuvenation. Although some products may have scientific rationale and produce visible results in the treatment of photoaging, they are not classified as drugs. As a result, these products are not subject to the rigorous testing or regulation by agencies such as the FDA. However, most cosmeceuticals do serve a role in keeping the skin moisturized and many are combined with topical retinol to enhance their antiaging benefits (Draelos 2011).

Alpha-Hydroxy Acids

Alpha-hydroxy acids (AHA) are compounds derived from dairy products (lactic acid), fruit (malic acid and citric acid), or sugar cane (glycolic acid). By definition, they contain one hydroxyl group attached to the alpha position of the acid. Topical treatment of photodamaged skin with AHA has been reported to improve wrinkling, roughness, and dyspigmentation within months of daily application (Ditre et al. 1996; Smith 1996; Stiller et al. 1996), although documentation is less rigorous than for the retinoids. Histologically, improvements included increased epidermal thickness, increased papillary mucopolysaccharides, improved elastic fiber quality, and increased collagen density. In the USA, AHA can be found in different cosmetic preparations at concentrations of up to 8%, but there are no limitations for AHA concentration in cosmetic preparations

in Europe (excluding Switzerland) (DiNardo et al. 1996). A new generation of AHA called polyhydroxy acids appear to have similar beneficial effects as well as antioxidant properties without the attendant irritation common to AHA (Rokhsar et al. 2005).

Antioxidants

Free radicals have long been studied as a contributor to aging and disease processes. Endogenous production of radicals from cellular metabolism and exogenous sources from ultraviolet radiation and pollution can damage the skin on the cellular and tissue levels. Although the body possesses an elegant defense system to prevent radical damage, this innate system can be overwhelmed and lead to a state of oxidative stress or immunosuppression and can even trigger carcinogenesis. Antioxidants can provide additional protection to neutralize reactive oxygen species from both endogenous and exogenous sources (Chen et al. 2012).

Vitamin C

Vitamin C is a water-soluble AOx, and it is the predominant AOx in the skin based on molar concentrations. Vitamin C neutralizes free radicals in aqueous compartments of the skin and also plays a role in regenerating vitamin E. Aside from serving as an AOx, it is also a cofactor for critical enzymes in collagen synthesis and can inhibit elastin biosynthesis to reduce elastin accumulation. It also reduces pigment darkening by inhibiting tyrosinase and maintains hydration by protecting the epidermal barrier of the skin (Campos et al. 2008). At the molecular level, addition of topical 1% vitamin C increases collagen synthesis and reduces MMP (collagenase) expression. Application of topical L-ascorbic acid has been shown to have photoprotective effects including the reduction of erythema, sunburn cell formation, and immunosuppression (Darr et al. 1992; Nakamura et al. 1997).

Vitamin E

Vitamin E is a lipid-soluble AOx. Its main function is to protect the cell membranes from oxidative stress. A multitude of animal and human studies have demonstrated a reduction in lipid peroxidation (Lopez-Torres et al. 1998), photoaging, immunosuppression, and photocarcinogenesis after topical vitamin E application (Bissett et al. 1990; Jurkiewicz et al. 1995). Vitamins C and E work in conjunction in an elaborate network of redox reactions to stave off oxidative stress. Vitamin C regenerates oxidized vitamin E at sites of lipid peroxidation. Oxidized vitamin C requires GSH for its own regeneration. In summary, endogenous antioxidant molecules clearly play an important role in cutaneous response to UV irradiation (Steenvoorden and Beijersbergen van Henegouwen 1999). Still, while promising new antioxidant candidates appear to decrease UV-induced detrimental effects in skin, additional long-term studies are required to establish the ability of topically applied or orally administered antioxidants in preventing photoaging and photocarcinogenesis.

Polyphenols

Other naturally occurring antioxidants include polyphenolic molecules like flavonoids and prozyanidine. Polyphenols are present in wine (white and red), green and black tea, fruits, and vegetables. Polyphenols of plant origin such as those present in green tea and curcumin, silymarin, and apigenin present in fruits and vegetables, when topically applied, demonstrate photoprotection against skin cancer and appear to reduce UV-induced DNA damage. Genistein, an isoflavone found in soybean, is a recognized inhibitor of tyrosine kinase, the enzyme that initiates cell surface receptor-mediated signaling. The polyphenol resveratrol, present in grapefruit, nuts, and red wine, shows potent anti-inflammatory effects in part by preventing the development of cutaneous hydroperoxides, reducing leukocyte infiltration into the skin (Rice-Evans 1999).

Melasma

Introduction

Melasma (sometimes referred to as chloasma or the mask of pregnancy) is a common acquired disorder of hyperpigmentation affecting millions of people

worldwide. While it is thought to be triggered or exacerbated by sun exposure and hormones, much remains to be understood about its pathogenesis. A thorough understanding of the etiology of melasma and the research tools available to study this condition are crucial to enhancing management and developing novel targeted therapies of this often frustrating condition for both the dermatologist and patient to treat (Vaneeta and Amit 2011). Found most commonly in women with Fitzpatrick skin phototypes III through V living in areas of intense ultraviolet (UV) light exposure, melasma is often difficult to treat and has a significant negative impact on patients' quality of life (Balkrishnan et al. 2003; Cestari et al. 2006, 2007; Freitag et al. 2008).

Epidemiology

Several studies from around the world have attempted to discern the prevalence of melasma in the general population. The reported prevalence ranges from 9% in Hispanics in the southern parts of the USA to 40% in Southeast Asian groups (Sivayathorn 1995). Melasma is cited as the most common pigment disorder among Indians (Pasricha et al. 2007) and the third most common pigmentary disorder in those with black skin (Halder et al. 1983). A multicenter survey of females from nine countries found that Fitzpatrick skin phototypes III and IV were most commonly affected and that African Americans were more likely to have a positive family history of melasma (Ortonne et al. 2009). It was also noted that 41% of women surveyed had onset of disease after pregnancy but before menopause. Importantly, only 8% noted spontaneous remission. Only 25% of patients taking oral contraceptives had an onset of melasma after starting their contraceptive. While melasma was thought to be a pregnancy- and contraceptive-related disorder in the past, recent studies show that in many patients it is a chronic disorder that may last for decades. Although common, there is much to learn about the epidemiology of melasma worldwide.

Pathogenesis

While the exact pathogenesis remains unknown, it is hypothesized that the condition may be induced by biologically active melanocytes (Sheth et al. 2011a, b). A genetic predisposition has been noted in several studies (Moin et al. 2006; Ortonne et al. 2009). Known exacerbating factors include pregnancy, the use of hormonal contraceptives, and UV light exposure. The latter may be due to UV-induced upregulation of melanocyte-stimulating cytokines. The more recent observation shows increased vascularity in affected skin as well as the increased expression of vascular endothelial growth factor in the epidermis (Kim et al 2007). UV light is a commonly reported initiating or exacerbating factor for melasma, likely because of its effects on melanocytes and on cytokine production. Melasma occurs in sun-exposed areas, and many patients report an increased severity of melasma with sun exposure. One reason for this appears to be that UV radiation induces melanocyte proliferation, migration, and melanogenesis. In addition, UV radiation can lead to the production of multiple cytokines, including interleukin-1, endothelin-1, alpha-melanocyte-stimulating hormone (a-MSH), and adrenocorticotropic hormone (ACTH) from keratinocytes, which in turn upregulate melanocyte proliferation and melanogenesis. Examining the local expression of cytokines in lesional and perilesional skin from 10 Korean women, Im et al. used immunohistochemistry to show that a-MSH was expressed to a greater degree in lesional melasma skin in the stratum spinosum and stratum granulosum than in perilesional skin. There was, however, no difference in the amount of melanocortin-1 receptor or ACTH expression. These findings suggest that sustained overexpression of MSH in lesional skin after UV exposure may be a significant factor for the development of melasma (Im et al. 2007).

The hormonal link to melasma is not clearly elucidated. Many patients note the onset or worsening of disease with pregnancy or oral contraceptive use, and several studies have sought to clarify the roles of particular hormones in the pathogenesis of melasma. Melanocytes from

healthy skin have been shown to express both nuclear and cytosol estrogen receptors. A study revealed by immunohistochemical staining that lesional melasma skin had increased estrogen receptor expression as compared to nearby normal skin (Liebermen and Moy 2008). In addition, incubation of melanocytes from normal skin with estradiol has been found to increase the proliferation of melanocytes but downregulate tyrosinase activity and melanogenesis (Jee et al. 1994). Interestingly, estradiol, estriol, and progesterone incubation led to increased cell proliferation, but to a lesser degree, and did not increase tyrosinase activity. It is still unclear why certain areas of the face are predisposed to developing melasma while others are not involved. Hormone receptors and blood vessels may play a role, but other factors, such as sebaceous gland density and activity, phototoxicity, and antioxidants, may also be involved. Therefore, while the link of melasma and the use of contraceptives is not well-established, it is prudent to stop the use of oral contraceptive pills and prevent its future use when possible (Sheth et al. 2011a, b).

Recent studies have also examined the possibility of a neural component to melasma (Bak et al. 2009).

Finally, melasma may also have a vascular component in its pathogenesis. Recent study found that biopsy specimens of lesional melasma skin had greater vascular endothelial growth factor expression in keratinocytes compared to nearby nonlesional skin (Kim et al. 2007). Additional work in this area is needed to help elucidate the underlying pathogenesis of this condition.

Clinical and Histological Features

Melasma is an acquired disorder of symmetrical hyperpigmentation appearing as light brown to dark, muddy brown macules and patches on the face (Fig. 6). Several clinical patterns of melasma have been described, but many patients have a mixture of these patterns. The centrofacial pattern is the most common and consists of lesions on the forehead, cheeks, nose, upper lip, or chin (Figs. 7 and 8). The malar pattern describes lesions located primarily on the cheeks and nose. The mandibular pattern consists of lesions on the ramus of the mandible (Mandry-Pagan and Sanchez 2000). This latter pattern may actually be a form of poikiloderma of Civatte, because patients are often postmenopausal and biopsy specimens reveal significant actinic damage. Although melasma of the forearms has been described, this entity is not always present in patients with facial melasma and has not been well characterized (O'Brien et al. 1997).

Melasma can be further classified based on a Wood's lamp examination to help identify the location of the pigment. Lesions that are enhanced when viewed under a Wood's lamp imply increased epidermal melanin content, whereas those that are not enhanced with a Wood's lamp examination imply an increase in dermal melanin content. Lesions that have both enhancing and nonenhancing areas are said to have a mixed pattern (Gilchrest et al. 1977). Recent histologic studies indicate that this construct may not be accurate.

Differential Diagnosis

Disorders that can be confused for melasma include postinflammatory hyperpigmentation, solar lentigines, ephelides, drug-induced pigmentation, actinic lichen planus, facial acanthosis nigricans, frictional melanosis, acquired bilateral nevus of Ota-like macules (Hori's nevus), and nevus of Ota (Trout et al. 2003). A careful history, an examination of the skin including a Wood's lamp and dermatoscopy examination, the recognition of concomitant inflammatory disorders, and a skin biopsy specimen in some cases are all helpful in making the correct diagnosis.

The Melasma Area and Severity Index

Good outcome measures are important in evaluating the effectiveness of therapies. Kimbrough-Green et al. created the Melasma Area and Severity Index (MASI) in an attempt to standardize its subjective evaluation (Kimbrough-Green et al. 1994). To calculate a MASI score (0–48),

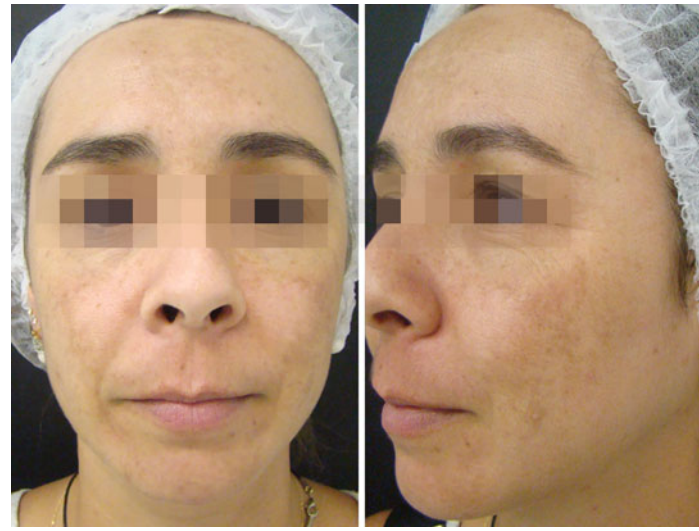

Fig. 6 Melasma: typical presentation in white woman phototype III

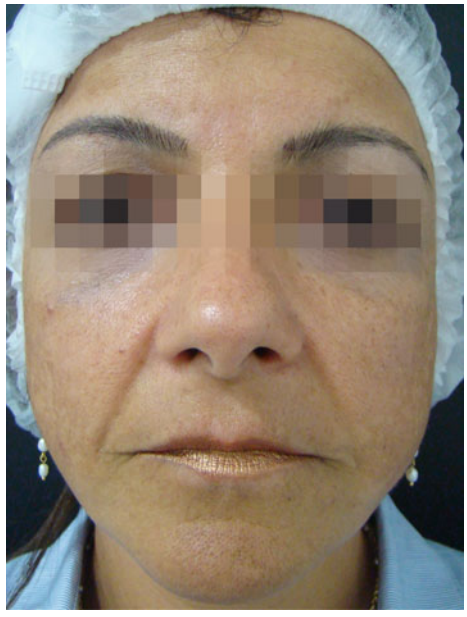

Fig. 7 Melasma: typical presentation in woman phototype IV

three factors must be subjectively assessed: the area (A) of involvement, darkness (D), and homogeneity (H) – in the forehead (f), right malar (rm), left malar (lm), and chin (c) region. Each region corresponds to 30, 30, 30, and 10% of the total face, respectively. The area of involvement in each of these four areas is given a numeric value of 0 to 6 (0 = no involvement; 1 = < 10%; 2 = 10–29%; 3 = 30–49%; 4 = 50–69%; 5 = 70–89%; and 6 = 90–100%). D and H are rated on a scale from 0 to 4 (0 = absent; 1 = slight; 2 = mild; 3 = marked; 4 = maximum). The sum of the severity ratings for D and H is then multiplied by the value of the areas of involvement for each of the four facial areas to obtain the MASI. While the MASI does demonstrate interrater reliability, the rating of individual components has proved to be problematic. Thus, more recently, a modified MASI (mMASI) score has been developed. The mMASI eliminates the homogeneity component of the calculation, making it more clinician-friendly. It also provides a new reference range (0–24). Area (A) and darkness (D) are scored as follows: area of involvement: 0 = absent, 1 = <10%, 2 = 10–29%, 3 = 30–49%, 4 = 50–69%, 5 = 70–89%, and 6 = 90–100%; darkness: 0 = absent, 1 = slight, 2 = mild, 3 = marked, and 4 = severe (Pandya et al. 2011).

It is imperative that clinicians understand and appreciate the significant emotional distress that may accompany this condition. Melasma may be clinically disfiguring, with profound flow-on effects for some of those affected. The most commonly used tool that reliably measures the effect of melasma on quality of life is the MelasQoL (Balkrishnan et al. 2003). This tool has been shown in several studies to be adaptable to various cultures. Given the significant impact on quality of life and the improvement in this measure with

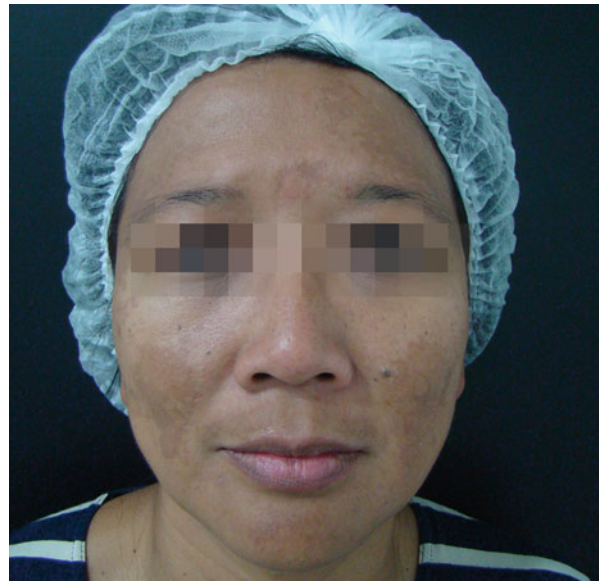

Fig. 8 Melasma in Asiatic patient

treatment, it is essential to ask the patient about the psychological impact of the condition on their life (Cestari et al. 2006; Cestari et al. 2007).

Treatment

Several methods of treatment exist for melasma but the condition is chronic and relapsing. Dark skin types (Fitzpatrick types IV to VI) are especially difficult to treat because of the increased risk of postinflammatory hyperpigmentation (PIH). There is no single, universally efficacious treatment. Thus, combination treatment is the best approach for challenging cases (Rodrigues and Pandya 2015). The cessation or avoidance of exacerbating factors such as use of hormonal contraception (Resnik 1967) and UV light exposure (Grimes 1995) is essential to successful treatment.

Topical Treatment

Photoprotection

Patients should be instructed to seek shade and avoid the sun, especially during the hours of 10 am to 3 pm; wear protective clothing, including long-sleeved shirts and broad-brimmed hats; apply and reapply a broadspectrum sunscreen with a sun-protection factor (SPF) of at least 30, in combination with a physical blocker such as titanium dioxide and avoid artificial UV light (Sheth and Pandya 2011a).

More recently, visible light (VL) has been implicated in development of melasma, especially in those with darker skin. One study found that although UVA-1 and VL can induce pigmentation in skin types IV–VI, the pigmentation induced by VL was darker and more sustained (Mahmoud et al. 2010). Opaque sunscreens (e.g., titanium dioxide or zinc oxide), especially with the addition of an absorbing pigment such as iron oxide, are more efficacious than chemical sunscreens in protecting against VL. Adding such an agent increases a sunscreen's photoprotective capacity that, in turn, increases the success of melasma treatment, compared with UV-blocking sunscreens alone. Thus, for difficult to treat cases, the application of sunscreen, especially opaque iron oxide-containing sunscreens, should be considered. In addition, use of computer screen protectors and tinted car windows should be considered. Cosmetic camouflage agents may be an important adjunct therapy. Many products exist for this purpose (Rodrigues and Pandya 2015).

Hydroquinone

Hydroquinone (1,4 dihydroxybenzene) inhibits the conversion of DOPA to melanin by inhibiting tyrosinase. This hydroxyphenolic compound has been used to treat hyperpigmentation for over five decades. Its mechanism of action involves its effects on melanosomes and the formation, melanization, and degradation as well as eventual necrosis of melanocytes (Jimbow et al. 1974). This compound's efficacy is undoubted (Ennes et al. 2000). It remains the gold standard treatment for epidermal melasma, though its effects are reversible. It is used in varying concentrations 2–5% and often in combination with other topical agents such as sunscreen, tretinoin, topical steroids, and kojic acid. Common side effects of hydroquinone (which are dose and duration dependent) in the short term include irritation, erythema, stinging, irritant or allergic contact dermatitis, and transient halo hypochromia in treated areas. In practice, the agents added to hydroquinone, such as tretinoin, glycolic acid, and sunscreens, are usually responsible for the excessive irritation. Intermediate and long-term side effects of hydroquinone may include the development of milia, paradoxical PIH (Prignano et al. 2007), and exogenous ochronosis.

The safety of the long-term use of hydroquinone has been widely debated. While the EU has banned its use as a cosmetic ingredient due to concerns over ochronosis and occupational vitiligo, prescription hydroquinone is still available to patients. The US Food and Drug Administration (FDA) have not yet removed over-the-counter products containing hydroquinone from the market (Rodrigues and Pandya 2015).

Retinoids

Various topical retinoids have proven to be efficacious in melasma therapy. Tretinoin is undoubtedly efficacious for melasma (Griffiths et al. 1993a). Multiple mechanisms of action are cited, including effects on keratinocytes, melanosomes and melanin synthesis, and the inhibition of tyrosinase transcription (Rodrigues and Pandya 2015). Topical tretinoin's use as monotherapy, however, is unlikely to be as effective as hydroquinone or combination therapy, being limited by side effects including erythema and irritation seen in 67–88% of patients (Gandhi et al. 2012) and requires a prolonged duration of treatment to achieve clinical improvement.

Combination Products

Topical therapy with a triple combination agent appears to be the most clinically effective initial therapy for patients with melasma. The Kligman formula (5% hydroquinone, 0.1% tretinoin, 0.1% dexamethasone) was one of the first combinations developed for hyperpigmentation over 30 years ago (Kligman and Willis 1975). This combination minimizes irritancy, maximizes effect in a shorter period of time than when the ingredients are used individually, prevents the oxidation of the hydroquinone, and improves the penetration of topical agents into the epidermis. Efficacy was reduced when any of the three components was eliminated.

Other dual and triple agent therapies have been studied. One of the most successful combination formulations has been 4% hydroquinone, 0.05% tretinoin, and 0.01% fluocinolone acetonide (Sheth and Pandya 2011b). Other combinations have also been evaluated with varying success such as hydroquinone, hyaluronic acid, and glycolic acid; 2% kojic acid, 10% glycolic acid, and 2% hydroquinone; and glycolic acid and hydroquinone alone (Rodrigues and Pandya 2015).

Azelaic Acid

Azelaic acid is derived from *Pityrosporum ovale* and is a weak reversible competitive inhibitor of tyrosinase (Lowe et al. 1998). Significantly greater improvement was seen in some studies, and the results were comparable to hydroquinone 2% and 4% (Verallo-Rowell et al. 1989). The most commonly reported side effects include erythema, burning, scaling, and pruritus (Balina and Graupe 1991; Farshi 2011).

Other Topical Agents

Ascorbic acid (vitamin C) is another reported treatment for melasma through its ability to

chelate copper ions (Huh et al. 2003). Unfortunately ascorbic acid is highly unstable, rapidly oxidized, and does not work well as monotherapy. Increased efficacy can be achieved by combining it with soy or licorice extracts. It is a good treatment adjunct in those who cannot tolerate hydroquinone as it causes less cutaneous irritation. Licorice extract (with active ingredients; liquiritin and isoliquiritin) inhibits tyrosinase and has anti-inflammatory properties. However, clinical data supporting its efficacy in melasma is lacking.

Arbutin/deoxyarbutin is hydroquinone derivative from Uva ursi folium (bearberry plant) and can be found in both blueberry and cranberry leaves. Treatment with 3% arbutin may lighten the skin but higher concentrations may cause hyperpigmentation (Draelos 2007). This agent has not been reported in the treatment of melasma, though it is listed as an ingredient in many over-the-counter skin lightening creams.

Tranexamic acid, also known as trans-4-aminomethylcyclohexanecarboxylic acid, is a plasmin inhibitor and lysine analog that has been shown to prevent UV-induced pigmentation in guinea pigs (Maeda and Naganuma 1998). In keratinocytes, it prevents the binding of plasminogen to keratinocytes, which leads to less free arachidonic acid and subsequent decreased production of prostaglandins. This in turn leads to a decrease in tyrosinase activity in melanocytes. Of note, topical tranexamic acid can cause allergy or irritation, so newer liposomal delivery systems have been created to improve tolerability. Intradermal tranexamic acid injections have been investigated in 100 patients with Fitzpatrick skin phototypes IV to VI and mixed or dermal melasma with good response (Lee et al. 2006).

Octadecenedioic acid, orchid extracts, magnolignan, mequinol, emblica extract, and soy have been studied for hyperpigmentation, but studies critically evaluating their efficacy in melasma are required before any recommendations can be made. Other new and experimental agents have been reported for pigmentation, including aloesin (a natural derivative of coumarin, derived from aloe vera flavonoids), ellagic acid, gentisic acid, hydroxycoumarin, and naturally derived botanical extracts. Silymarin, alpha lipoic acid, green tea, cinnamic acid (found in ginseng and cassia plants), and a novel formulation pyronyl acrylic acid esters 3a–i are also on the extensive list of possible future treatments for pigmentation. However, human trials are needed for these agents to assess efficacy (Fisk et al. 2014).

Systemic Therapy

Tranexamic Acid

Oral TXA, while traditionally used for bleeding diatheses and menorrhagia, has now been successfully employed, especially in Japan, for the treatment of melasma (Cho et al. 2013). TXA-containing tablets are also popular beauty foods available over-the-counter in Korea for the purpose of whitening the skin. Though its mechanism of action is not entirely known, mechanisms such as decreased tyrosinase activity in melanocytes and possible increases in vascular endothelial growth factor and alpha-melanocyte-stimulating hormone have been discussed (Shin et al. 2013). It has been used in topical and intradermal forms but several reports suggest that oral TXA in doses of 500 or 750 mg daily is a potent and convenient modality for melasma treatment. Na and Choi have shown clinical and histological improvement of pigmentation when this doses were used for 8 weeks (Na et al. 2013). The most commonly reported side effects are headaches, menstrual irregularity, nausea, and back pain. Studies in women's health literature have found that even in doses up to 3.9–4 g/day (for 4–5 days per cycle), adverse effects are few and mild. No evidence exists to support an associated increased risk of thrombotic events when these doses for melasma are used (Leminen and Hurskainen 2012). Larger studies are required to more fully evaluate this therapeutic option for melasma.

Polypodium Leucotomos

Orally administered *Polypodium leucotomos* may provide protection against the detrimental photoaging effects of sunlight and can also help reduce the frequency and severity of polymorphous light

eruption. *Polypodium leucotomos* 250 mg twice daily has also been shown to be beneficial for the prevention and potential treatment of several aesthetically relevant conditions such as melasma (Nestor et al. 2014).

Pycnogenol

Pycnogenol is a standardized extract of the bark of the French maritime pine (*Pinus pinaster*) a well-known, potent antioxidant. Studies show that pycnogenol 25 mg three times daily is therapeutically effective and safe in patients suffering from melasma (Ni et al. 2002).

Acne

Introduction

Acne is one of the most frequent skin diseases and is now considered to be a chronic and relapsing inflammatory condition which varies in severity and may require long-term treatment (Gollnick 2015). Although acne is not associated with severe morbidity, and mortality, the resulting scars in the most severe cases can produce serious emotional disturbances such as anxiety, depression, and low self-esteem. In adolescents the deterioration of quality of life may be greater than in conditions such as asthma and epilepsy (Mallon et al. 1999). An effective treatment can drastically impact the patient quality of life and should be established early to minimize possible cutaneous and emotional scars.

Epidemiology, Genetics, and Environmental Factors

Acne is estimated to affect 9.4% of the global population, making it the eighth most prevalent disease worldwide (Tan and Bhate 2015). It is the most common skin disorder occurring universally, with an estimated prevalence of 70–87% (Dreno and Poli 2003). Epidemiological studies have demonstrated that acne is most common in postpubescent teens, and the boys are most frequently affected, particularly with more severe forms of the disease. However, acne may persist beyond adolescence in a significant proportion of individuals, particularly women (Nast et al. 2012)

Genetic factors have been recognized. Several genes are believed to be involved, of which only the gene for cytochrome P-450-1A1 and the gene for steroid 21-hydroxylase (which influences androgen production in the adrenal gland) are documented (Herane and Ando 2003). There is a high concordance among identical twins, and there is also a tendency towards severe acne in patients with a positive family history for acne (Burkhart and Burkhart 2007; Nast et al. 2012).

Even today there are myths and misconceptions about acne. On the other hand, recently some ideas regarded as myths have been supported by scientific evidence. Although few reliable studies correlate diet with acne, there is a difference in prevalence between industrialized and nonindustrialized societies, suggesting it as a factor to consider. Recently, it was found a relationship between intake of foods with high glycemic load and the pathogenesis of acne by hyperinsulinemia caused by such foods (Smith et al. 2008; Kwon et al. 2012).

Since long has been evoked the causal relationship between the stress and acne, but just recently, it was demonstrated a positive correlation between the aggravation of acne and the existence of high levels of stress during the period of school exams (Chiu et al. 2003).

There is no evidence of a positive effect of exposure to sunlight on acne. Recent findings suggesting effectiveness of different spectra of artificial light cannot be generalized directly to natural sunlight. In addition, photosensitivity is a problem with the treatments commonly used in acne, such as tetracyclines and isotretinoin (Magin et al. 2005).

Pathogeneses

Acne is a multifactorial disease, which originates in the pilosebaceous unit. Four main factors are involved in its pathogenesis: sebum production, disturbed keratinization within the follicle, *Propionibacterium acnes* follicular colonization,

and the release of inflammatory mediators into the skin. Although the chain of events is still to be fully understood, it is believed that the first phase of this process is the formation of the microcomedo, which is the precursor to comedones, papules, and pustules (Cunliffe 1980).

Patients with seborrhea and acne have a significantly greater number of lobules per gland compared with unaffected individuals. Androgens such as dihydrotestosterone (DHT) and testosterone have been shown to stimulate the proliferation of sebocytes from the face, but not the leg, and this differential response may account for the specific localization of acne lesions. Not long ago it was suggested that the sebocyte activity is controlled by several pathways and hormones besides the androgens like, for example, peroxisome proliferator-activated receptors, substance P receptors, alpha-melanocyte-stimulating hormone, insulin-like growth factor, corticotropin-releasing hormone, vitamin D, and ectopeptidases (Deplewski and Rosenfield 2000).

The microcomedo is formed by the sebaceous hypersecretion, increased proliferation, and reduced shedding of intrafollicular keratinocytes that accumulate in the sebaceous follicles leading to its obstruction. As sebum and keratinocyte debris accumulate in the microcomedo, larger, clinically visible closed or open comedones develop (Gollnick 2015). This altered keratinization may be related to decrease of linoleic acid in sebum, the proliferation of type 1 5α-reductase in the infundibulum, and abnormal lipidic inclusions linked to defects in corneocytic differentiation (Montagner and Costa 2010). This altered sebum triggers the liberation of interleukin-1 (IL-1), by infundibular keratinocytes. The interleukin-1a upregulation contributes to the development of comedones independent of the colonization with *P. acnes* (Nast 2012).

A recent genetic study on the populations of *P. acnes* indicates that particular clones of *P. acnes* play an etiologic role in acne while others are associated with health (Lomholt and Kilian 2010). This finding reinforces the hypothesis that there are species of truly pathogenic *P. acnes* what supports the classically used antibiotic therapy in the treatment of acne (McDowell et al. 2012). The colonization of the infra-infundibulum of follicles by *P. acnes* contributes a lot to the development of inflammatory lesions. *P. acnes* secretes lipases, which degrade triglycerides, and proteases that damage the follicular wall and trigger inflammation with the release of chemotactic factors, that firstly recruit CD4-lymphocytes, and later neutrophils and monocytes to the affected area. *P. acnes* also activates markers of the innate immune system such as Toll-like receptor 2 (TLR-2) on monocytes, and this induces the production of proinflammatory cytokines such as interleukin-8 (IL-8) and matrix metalloproteinase that subsequently leads to the recruitment of neutrophils into the pilosebaceous unit (Beylot et al. 2014). *P. acnes* also induces follicular keratinocytes to release IL-1a leading to keratinocyte proliferation and comedone formation. Recent research has shown that *P. acnes* may be present in the infundibulum of sebaceous follicles in large macrocolonies or biofilms. These biofilms may affect the responsiveness of *P. acnes* to antibiotics and increases the adhesiveness of the disturbed shedding keratinocytes expanding the comedogeneisis (Burkhart and Burkhart 2007).

Clinical Aspects

Acne presents as a polymorphic disease which occurs mostly on the face but might extend in few cases to the back and anterior region of the trunk. As mentioned, the basic and initial lesion is the microcomedo, which is not a visible lesion. The characteristic lesion is the comedo, which can be closed, with whitish aspect, usually measuring from 1 mm to 2 mm, or open, blackened color due to the oxidation of fats and increased deposition of melanin (Fig. 9). Superficial inflammatory lesions consist of erythematous papules around the comedos that may evolve with the formation of pustules (Fig. 10). Deeper inflammatory lesions as cysts, nodules, and abscesses account for an advanced phase of acne, with varying sizes (Fig. 11). These frequently drain pus and leave scars, which may be a natural consequence of the healing of inflammatory lesions.

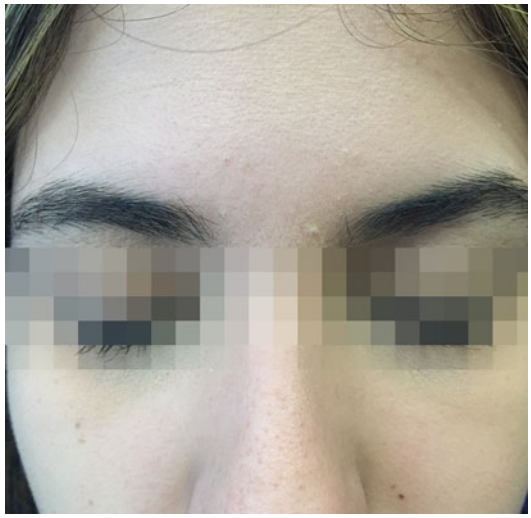

Fig. 9 Open and closed comedos

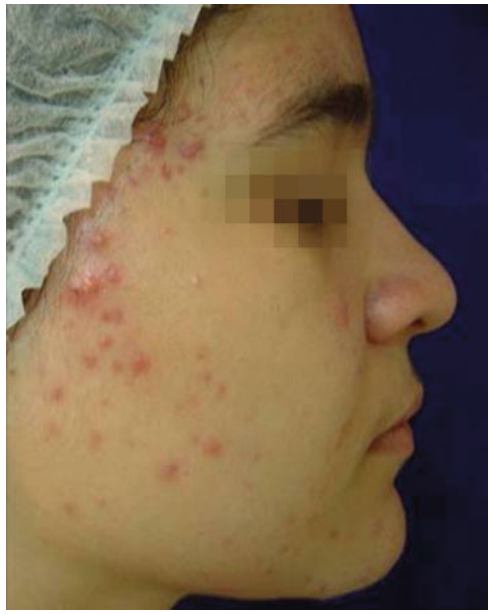

Fig. 10 Inflammatory acne with papulopustular lesions

Some classifications have been proposed and were based on the type of lesions (inflammatory and noninflammatory) and on the severity, establishing grades of I to V. In the grade I, the lighter form of noninflammatory acne, or comedoniana, is characterized by the presence of closed comedones (blackheads) and open comedones. Inflammatory lesions are present in the other degrees. On acne II there is a predominance of papules and pustules in addition to the comedones. In grade III acne, nodules and cysts can be observed. Acne conglobate, or grade IV, is a severe form with multiple inflammatory nodules, formation of abscesses and fistulas. Acne fulminans, or grade V, is a rare and severe form, abrupt, accompanied by installation systemic manifestations (fever, leukocytosis, and arthralgia).

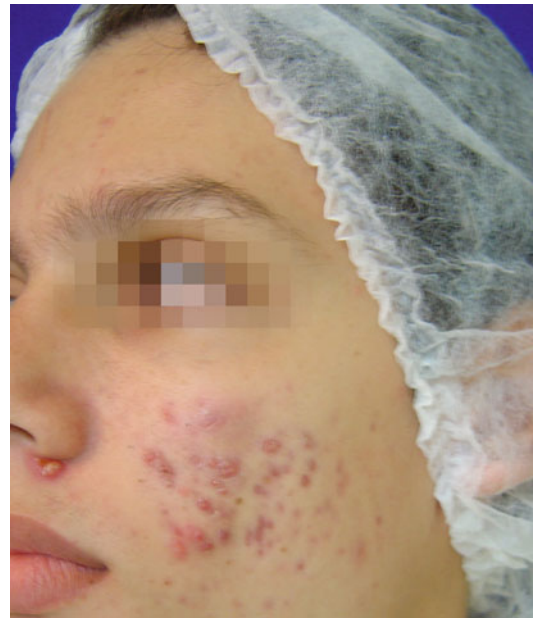

Fig. 11 Inflammatory acne with nodular lesions

Differential Diagnosis

The formation of comedones is intrinsic to the diagnosis of acne vulgaris and when not clinically apparent, alternative diagnoses should be considered. The commonest mistaken diagnosis is rosacea, which occurs in an older group and lacks comedones. Acneiform eruptions are not restricted to the face, usually affect the trunk and, as in rosacea, there are no comedones. In perioral eczema there may be pruritus, the lesions tend to be drier and also there are no comedones (Zaenglein et al. 2008).

Table 1 Acne treatment algorithm. Based on Thiboutot D,Gollnick H,Bettoli V,Dréno B,Kang S,Leyden JJ, et al. New insights into the management of acne: An update from the Global Alliance to Improve Outcomes in Acne Group. J Am Acad Dermatol. 2009;60(5 suppl):S1-50

	Mild acne		Moderate acne		Severe acne
First choice	Comedogenic	Papulopustulosa	Papulopustulosa	Nodular	Nodular/ conglobate
	Topical retinoid	Topical retinoid+ topical antimicrobial	Oral antibiotic+ topical retinoid +/− BPO	Oral antibiotic+ topical retinoid+ BPO	Oral isotretinoin
Alternative	Alternative topical retinoidor azelaic acid	Alternative topic antimicrobial+ alternative topical retinoid or azelaic acid	Alternative oral antibiotic+ topical retinoid +/− BPO	Oral isotretinoin oralternative oral antibiotic+ alternative topical retinoid +/− BPO/azelaic acid	High dose oral antibiotic+ topical retinoid + BPO
Alternative for females			Antiandrogens+ topical retinoids/azelaic acid +/− antimicrobial topic	Antiandrogens+ topical retinoid +/oral antibiotic+/− Alt antimicrobial	High dose oral antiandrogen+ Topical retinoid +/− Alt topical antimicrobial
Alternative in pregnancy	Postpone treatment for after breastfeedingor BPO or azelaic acid		Oral stearate erythromycin+ BPO or azelaic acid		
Maintenance	Topical retinoid		Topical retinoid + BPO		

Treatment

First of all, education of the patient as in any chronic disease is critical to the success of the treatment. The patient's knowledge about the pathophysiology and chronicity of acne is a fundamental strategy to ensure patient compliance and achieve the best therapeutic results.

In therapeutic approach various factors are considered, but the classification of type and severity is fundamental in this decision. Most classifications are based on the predominance of elementary lesions (comedos, papules, pustules, and nodules) and in the number, size, and extension of the lesions. The latest recommendations from the Global Alliance to Improve Outcomes in Acne are summarized in the algorithm described in Table 1 (Thiboutot et al. 2009).

Topic Treatment

Retinoids

The topical retinoids are the mainstay of treatment of comedonal acne since they are the drugs that exert the more powerful action in the control of comedogeneses. They normalize follicular keratinocyte differentiation and cohesion of corneocytes preventing the formation of microcomedones (Das and Reynolds 2014). Through the regularization of the keratinization process, retinoids favor the penetration of other drugs such as antibiotics and benzoyl peroxide (BPO), into the deeper parts of the pilosebaceous unit (Gollnick 2015). Topical retinoids also have direct and indirect anti-inflammatory effects (Schmidt and Gans 2011).

In addition, the retinoids also act on postinflammatory hyperpigmentation which is a common outcome of acne primarily in patients with highest phototypes. The most frequently used are tretinoin (0.01 a 0.1%), isotretinoin (0.025 a 0.1%), and adapalene (0.1 a 0.3%), all showing similar comedolitic activity. The preferred vehicle must be the microsphere gel which is less annoying than the conventional gels, but does not have the power of follicular occlusion of the creams, which should be avoided (Rao et al. 2009; Kircik 2011). Most retinoids are photodegradable molecules and therefore should

be applied at night. The main drawback to the majority of topical retinoids is that they have potential cutaneous adverse effects, such as erythema, scaling, dryness, burning, and pruritus. Retinoids may also cause acne flaring defined as a transient increase in pustule formation via expulsion of comedones during the first few weeks of treatment. This phenomenon occurs in up to 20% of patients treated with retinoic acid and isotretinoin (Gollnick 2015). To minimize possible irritation they should be applied preferably in the evening and about half an hour after washing the face with mild cleansing agent. Very sensitive patients must be warned about the potential irritation, the possibility of transitional aggravation in 2 weeks and instructed to start treatment with applications on alternate days. If irritation occurs, treatment should be interrupted until improvement then restarted. In patients with sensitive skin, adapalene may be preferable since it has a comparable efficacy to tretinoin 0.025%, with a low irritancy potential due to its intrinsic anti-inflammatory activity. Adapalene is also more stable to light which allows its application in the morning (Katsambas et al. 2004). Topical retinoids are still contraindicated in pregnancy, and women of childbearing age must use effective contraception while on treatment (Gollnick 2015).

Benzoyl Peroxide (BPO)

Benzoyl peroxide (BPO) is a substance classically used in the treatment of acne, and its main action is to reduce the number of *P. acnes* via oxidative mechanisms. It also has anti-inflammatory action and even a comedolitic weak action (Gollnick 2015). Topical formulations are available in 2.5%, 5%, 10%, and 20% concentrations, but it is recommended to use PB in low concentrations (2.5% or 5%); once its effectiveness enhances a bit with higher concentrations, the cutaneous intolerance greatly increases (Williams et al. 2012). The main advantage of BPO compared with topical antibiotics is that BPO is not associated with the development of bacterial resistance. An association often recommended is that of PB with topical antibiotic or oral, because the bactericidal action of the PB promotes a smaller development of bacterial resistance and better tolerability, and both drugs act synergistically in reducing the *P. acnes* (Thiboutot et al. 2009). Patients should be advised that it can cause bleaching of hair, clothes, and bed linens (Gollnick 2015).

Azelaic Acid

Azelaic acid inhibits the synthesis of cellular protein in aerobic and anaerobic microorganisms, especially *P. acnes* and *S. epidermidis*. As an antimicrobial agent, it helps normalize follicular ostium keratinization. A great advantage is that it is safe to use during pregnancy and breastfeeding (Montagner and Costa 2010). It may be especially useful during the summer months, because it does not produce phosensitization. Azelaic acid may be an option in patients who do not tolerate retinoids. The resulting hypopigmentation of azelaic acid can be beneficial for dark skinned patients with postinflammatory hyperpigmentation (Katsambas et al. 2004).

Antibiotics

The main mechanism of action of topical antibiotics is to reduce the population of *P. acnes* in the pilosebaceous duct. The most used are clindamycin at 1% and erythromycin at 2–4%. These agents are generally well tolerated and the main concern lies in microbial resistance. The efficacy of erythromycin, in particular, may be declining due to bacterial resistance (Simonart and Dramaix 2005). A study showed that in addition to increased levels of antibiotic-resistant propionibacteria, topical erythromycin 2% also produces an increase in the number of other antibiotic-resistant bacteria such as staphylococci (Mills et al. 2002).

Systemic Treatment

The systemic treatment should be preferred in the most serious cases, which do not respond to topical therapy, or in patients with higher risk of scarring.

Oral Antibiotic

Tetracyclines are the first-line antibiotics, given its advantages in terms of efficiency, safety, and

Table 2 Oral antibiotics in acne

Options levels	Antibiotic	Dosage	Side effects
First line	Tetracycline	250–500 mg 2×/day	Gastrointestinal intolerance Decreased absorption in presence of foods
	Doxycycline	50–100 mg 2×/day	Gastrointestinal intolerance Photosensitivity
	Limecycline	150–300/day 1×/day	Gastrointestinal intolerance
	Minocycline	50–100 mg 2×/day	Gastrointestinal intolerance Vestibular disturbances Skin pigmentation Lupus erythematosus
Second line	Erythromycin	500 mg 2×/day	Gastrointestinal intolerance
Third line	Sulfametoxazol trimetropim	800/160 2×/day	Gastrointestinal intolerance
??????	Azithromycin	500 md/day 3 day/ week	Gastrointestinal intolerance

microbial resistance. First-generation tetracyclines are given in a dosage of 500 mg every twelve hours and is best taken on an empty stomach. The second-generation ones provide faster effect and do not suffer influence of feeding. Doxicycline and minocycline are used in 100–200 mg/day dosage, which should be reduced slowly as soon as improvement is achieved. Limecycline is given in 150–300 mg/day. Gastrointestinal intolerance is a side effect of tetracyclines and erythromycin. Tetracyclines also might lead to discoloration of the dental enamel in children under 10 years old. Minocycline has been associated with vestibular disorders, deposition of pigment, and, rarely, drug-induced lupus erythematosus, which usually occurs at the beginning of the treatment. Tetracyclines may cause pseudotumor cerebrii and must not be combined with systemic retinoids because this association may increase this probability (Montagner and Costa 2010). Doxicycline can cause photosensitivity. Sulfamethoxazole-trimethoprim 800/160 mg/day can be used as third-line agent.

A pulse therapy with azithromycin administered in doses of 500 mg/day for 3 days, in a total of three intermittent cycles, with 7-day intervals was introduced in the last 15 years. This therapeutic scheme proved to be effective, well tolerated, and had great acceptance by patients. However, its long plasma half-life, which keeps a persistent subinhibitory concentration, contributes to streptococcal resistance and therefore its use is not yet a consensus (Antonio et al. 2008; Montagner and Costa 2010). Oral antibiotics, dosages, and side effects are summarized in Table 2.

The evidence of bacterial resistance with the use of topical and/or systemic antibiotics led the Global Alliance to Improve Outcomes in Acne to recommend the rational use of antibiotics to prevent the development of bacterial resistance. The first recommendation is do not use topical antibiotic as monotherapy, always add the benzoyl peroxide or retinoids. The second is to limit the use of antibiotics to short periods and discontinue when there is no further improvement or the improvement is only slight. Oral antibiotics should ideally be used for 3 months, but 6–8 weeks into treatment might be a sufficient time point to evaluate response to antibiotic. And the third is to avoid the concomitant use of oral and topical antibiotic, especially if chemically different because there is an increased risk of bacterial resistance and no synergistic action (Thiboutot et al. 2009; Nast et al 2012; Gollnick 2015).

Hormonal Therapy

Most patients that keep acne in adulthood are women, and androgens have great role in this. A traditional view of the adult female acne consists of predominant inflammatory lesions in the inferior third of the face. This classic view was

recently confronted by a study with 374 women with acne. It was observed that 90% of women had acne involving multiple areas of the face. Most of the women had both noninflammatory and inflammatory lesions with only 6.4% showing inflammatory lesions exclusively and 17.1% only comedonal acne. Still, only 11.2% had acne located specifically in the mandibular region (Dreno et al. 2014).

Besides acne, other signs of hyperandrogenism may be present as: androgenetic alopecia, hirsutism, menstrual disorders, ovulatory dysfunction with infertility, and insulin peripheral resistance. These signs or symptoms deserve an investigation of an underlying hormonal disorder. The most common cause of hyperandrogenism is polycystic ovary syndrome (80%), but the differential diagnosis includes androgen-secreting neoplasm (adrenal gland or ovary), nonclassic congenital adrenal hyperplasia, the syndrome of hyperandrogenism, insulin resistance, acanthosis nigricans (HAIR-AN), the syndrome of seborrhea, acne, hirsutism and alopecia (SAHA), and exogenous androgens (testosterone, DHEA) (Kamangar and Shinkai 2012). In polycystic ovary syndrome, the main cause of hyperandrogenism, 70% of the patients have acne. However, in most cases a hormonal disorder is not found, what could be explained by a greater sensitivity of hormone receptors of sebocytes and keratinocytes to lower levels of androgens. Another important factor in the pathogenesis of female adult acne is chronic activation of innate immunity in skin that can be promoted by the long duration of acne and high levels of p acnes resistant selected by prolonged use of topical and systemic antibiotics (Dreno 2015).

Oral Contraceptives

The first option in hormonal therapy used to treat adult female acne when peripheral hyperandrogenemia is noted specifically with flare-ups before menstruation are the oral contraceptives. They inhibit the secretion of gonadotrophins, ovarian or adrenal androgens, as well as stimulate the hepatic synthesis of sex hormone-binding globulin (SHBG), leading to a lower plasmatic concentration of free testosterone. They also reduce the levels of IGF-1 and 5α reductase (Montagner and Costa 2010).

The third-generation progestins have the lowest androgenic activity and so are preferred to progestins with intrinsic androgenic activity which may cause worsening of acne (Dreno 2015). Combined oral contraceptives containing an estrogen (ethinyl estradiol) associated with a third-generation progestin (desogestrel, norgestimate and gestodene), or antiandrogen (chlormadinone, cyproterone, dienogest, trimegestone and drospirenone), are the best choices. Contraceptives only with progestogen, including levonorgestrel releasing intrauterine device (IUD), often worsen the acne and should be avoided in women with acne without contraindications to estrogens.

Spironolactone

Spironolactone may be added to contraceptive therapy if there is no improvement in acne after 3–6 cycles. Spironolactone which has antiandrogenic activity (due to inhibition of 5-alpha reductase) is typically reserved for adult females with acne that is refractory to conventional treatment (Dreno 2015). The usual dose can vary from 100 to 200 mg/day. However, lower doses of 50–100 mg daily often produce good clinical results and have the advantage of fewer side effects (Shaw 2000). A 8 year follow-up study evaluated the safety of spironolactone and the most common side effects were menstrual irregularities (22%), tiredness (16.5%), and breast tenderness (17%), all of which were mild and rarely caused cessation of the medication (Shaw and White 2002). If patients are using spironolactone as monotherapy, then adequate contraception needs to be used to avoid exposure to the drug during pregnancy since this can lead to male fetal abnormalities. The therapeutic response usually occurs within 2 months of starting therapy (Dreno 2015).

Isotretinoin

Isotretinoin (13-cis-retinoic acid) was approved by the US Food and Drug Administration (FDA) in 1982 for treatment of severe recalcitrant nodular acne. Isotretinoin revolutionized the treatment

of acne because it acts in its four major pathogenic factors: it greatly reduces sebaceous gland activity and size, which modifies follicular microclimate leading to downgrading *P. acnes* proliferation, and decreases Toll-like receptor-2 (TLR2) expression on circulating mononuclear cells that is persistent for several months posttherapy. Due to its excellent efficacy in acne, isotretinoin has been used not only in cases of nodular acne but also in refractory cases of severe nonnodular inflammatory acne and/or in patients with a family history of acne and scars (Leyden et al. 2014).

The minimum treatment duration is 5 months, depending on the daily dose and the patient's weight, with a minimum total dose of 120 mg/kg that could reach 150 mg/kg. Different dosage regimens of systemic isotretinoin had been evaluated. A low daily dose (0.1 mg/kg/day), intermediate daily dose (0.5 mg/kg/day), and high daily dose (1 mg/kg/day) showed similar effectiveness in clearing most patients' lesions by the end of the treatment. However, the dose directly influences the rate of remission, with larger doses reaching greatest periods of remission (Leyden et al. 2014).

An apparent flare-up may occur with increased development of inflammatory lesions around the fourth week of the treatment, which usually improve spontaneously. If the flare-up is very intense (resembling acne fulminas), it may be necessary to use 0.5–1 mg prednisolone/kg for 4–6 weeks and decreased dosage of isotretinoin with later gradual reintroduction. In very severe disease, oral prednisolone should better precede for 2–4 weeks the introduction of isotretinoin (Katsambas et al. 2004). In most cases of acne, start with the dose of 0.5 mg/kg in the first month and up to 1 mg/kg in the second month could be the best conduct. If the daily dose is lowered (based on mg/kg), the length of the treatment course would need to be extended by the amount that allows for reaching the target cumulative dose (Leyden et al. 2014).

Oral isotretinoin treatment is strictly contraindicated in pregnancy, the lactation period, and in severe hepatic and renal dysfunction. Hyperlipidemia, diabetes mellitus, and severe osteoporosis are relative contraindications. Some drug interactions should be avoided: vitamin A increases toxic effects of retinoids, the concomitant use with tetracycline can induce pseudotumor cerebri, and high doses of aspirin may enhance mucosal damage.

The most common side effects are dry lips or cheilitis, drying of the nasal mucosa, xerophthalmia, skin xerosis, and alopecia minor. It can also be observed less frequently with headache, joint pain, muscle pain (especially in athletes), and insomnia. Increased cholesterol, triglycerides, and liver enzymes can occur and should be examined throughout the treatment.

In relation to psychiatric manifestations some uncertainty persists because the visions of the specialties diverge. The psychiatric literature argues for a causal link between isotretinoin and depression. The dermatological literature suggests that acne is an independent risk factor for depression and isotretinoin can improve depression while treating acne and enhancing self-image. For this reason the current recommendation is to investigate previous psychiatric histories and check psychiatric state during and after the treatment (Rowe et al. 2014; Ludot et al. 2015).

The most important adverse effect is teratogenicity, and so it is important to exclude the risk of pregnancy before the administration. The use of oral contraceptives should be maintained throughout the course of treatment and up to 30 days after the last dose.

Despite the great effectiveness of isotretinoin, a second or even a third course treatment may be necessary. The requiring of a retreatment varies among different series but might reach to 41% of patients needing a second course of oral isotretinoin (Azoulay et al. 2007). The daily dose (mg/kg/day), duration of the course of therapy, and total drug exposure expressed as cumulative dose (total mg/kg) all directly influence the risk of relapse after an initial course of oral isotretinoin (Leyden et al. 2014).

Treatment During Pregnancy

During pregnancy the ideal would be to defer the treatment for after the breastfeeding. If it is not possible, an approach with topical agents should be preferred. Among topical medications,

erythromycin, BPO, and azelaic acid are safe options. In severe cases the oral erythromycin is the safest option (Gollnick et al. 2003).

Retinoid-Based Combination Therapy

The Global Alliance and the latest guidelines from the European Dermatology Forum recommends combination therapy with a topical retinoid and an antimicrobial agent as the preferred approach for almost all acne patients. This combination targets the majority pathogenic factors and results in a faster clearance of both inflammatory and noninflammatory acne lesions than either monotherapy alone (Thiboutot et al. 2009; Nast et al. 2012). If this combination is used as a fixed-dose combination product, it increases patient convenience in comparison with the need to apply two separate medications at different times of the day, which translates into greater adherence to treatment with faster improvement (Gollnick 2015).

In two large series with 517 and 1670 patients, the topical use of adapalene 0.1% combined with BPO 2.5% in a single product demonstrated superior results when compared to monotherapy or to the isolated use of the vehicle (Thiboutot et al. 2007; Gollnick et al. 2009).

A triple topical therapy using a retinoid combined with BPO and clindamycin has been recently proposed with good results but are awaiting more studies regarding safety (Bowman et al. 2005, Del Rosso 2007).

Maintenance Therapy

Today the chronicity of acne is well recognized and rebounds after discontinuation of a topical retinoid are common. In this way, the strategy for the treatment of acne includes an induction phase, followed by a maintenance phase to reduce the potential for recurrence of lesions and should be considered as part of the routine of acne treatment. Retinoids are the drug of choice for maintenance therapy because it decreases the number and prevents the development of microcomedos. In some cases it may be necessary to add an antimicrobial agent, in this case the BPO should be preferred. Most studies on maintenance therapy was made with adapalene and lasted about 3–4 months. The clinical experience indicates that the time required for maintenance can be much larger; future studies will define the best treatment regimens and the time required (Nast et al. 2012).

Other Therapeutics Modalities

Radiofrequency, light, and laser devices have been used in acne with good response on inflammatory lesions, possibly by their action on *P. acnes*. Blue light treatment is FDA-approved for acne treatment. Initial studies have been demonstrated to reduce the number of inflammatory, but not comedonal, acne (Das and Reynolds 2014). The combined use of the blue and red lights behaves in a synergic way due to their respective antibiotic and anti-inflammatory properties. Preliminary studies indicate that this combination is a promising and safe option in the treatment of acne (Paschoal and Ismael, 2010). Photodynamic therapy (PDT) has been used successfully in inflammatory lesions lasting for 3–6 months, with improvement observed in repeat treatment. Pulsed dye lasers (PDL) cause selective photothermolysis of dilated blood vessels within acne lesions and its main action may be the upregulation of cytokines mediate an anti-inflammatory effect that manifests as a global improvement in acne appearance rather than limited to the treated site.

Despite these encouraging results with medical devices for acne, double-blind randomized studies with a sufficient number of patients and comparisons devices with standard therapy (topical and systemic drugs) are missing. To date, they should only be seen as useful aids in inflammatory lesions in acne (Das and Reynolds 2014).

Rosacea

Introduction

Rosacea is a common inflammatory dermatosis located mainly on the face and is characterized by a chronic course of exacerbations and

remissions on a background of highly sensitive skin. Unlike acne vulgaris predominates after 30 years, although some cases have been described in childhood. Rosacea also has a negative impact on quality of life through stigmatizing feelings and anxiety of patients (Elewski et al. 2011).

Epidemiology

In Europe, there is an increasing prevalence from south to north: in Germany Kingdom, a large epidemiological study calculated an incidence rate of 1.65 per 1000 person-years, with 80% of rosacea cases affecting individuals over 30 years of age (Spoendlin et al. 2012). There are some gender differences, since rosacea usually starts earlier among females and rhinophyma is almost exclusively seen among males. People with lower phototype are more affected (Millikan 2009).

Pathogeneses

Despite the progress achieved by current research, the pathophysiology of rosacea is not completely understood. Recent findings revealed that the sensory and autonomic nervous systems and the innate immune system are overstimulated promoting a chronic pathological inflammatory state (Weinkle et al. 2015).

Currently intimate relationship between the physical barrier of the epidermis and some innate immune functions of the skin has been established. Studies in mice showed that defects in innate immune gene expression lead to defects in the physical barrier and in atopic dermatitis defects in elements of the physical barrier lead to abnormalities in skin immune function (Yamasaki et al. 2011).

Recent findings have shown that rosacea patients present excessive activation of innate immune effector molecules. Some of these are cathelicidin, antimicrobial peptides, and increased expression and activity of the serine protease kallikrein 5 (KLK5) (Yamasaki et al. 2007). Toll-like receptors (TLRs) are pattern recognition receptors bound to innate immunity which expression is increased in rosacea (Yamasaki et al. 2011). The overexpression of TLR2 enhances the production of cathelicidins and its processing enzyme KLK5. Cathelicidin LL-37 has been extensively involved in describing the pathogenic inflammatory response, impaired antimicrobial activity, and vascular dysfunction of rosacea. That abnormal TLR2 function would explain the inappropriate enhanced inflammatory responses to environmental stimuli and could act as a critical element in the pathogenesis of rosacea (Weinkle et al. 2015).

Demodex folliculorum is a mite that inhabits the hair follicles, lies in increased number in papulopustular rosacea, and classically has been implicated in its pathogenesis. Current knowledge allows us to infer that it could be a trigger of an inflammatory process due to an altered immune response that includes the overexpression of TLR2. In addition, *Demodex folliculorum* could act broadcasting other bacteria such as *Flavobacterium* spp, *Bacteroides* spp (Holmes 2013), and *Bacillus oleronius* (Lacey et al. 2007) that could exacerbate the inflammatory process.

The persistent erythema observed in rosacea reveals a vascular disorder. Molecules that control vascular response like vascular endothelial growth factor (VEGF) and vasoactive intestinal peptide (VIP) are super expressed in rosacea. Rosacea skin has a significantly lower heat pain threshold than normal skin. The transient receptor potential ion channels of the vanilloid type (TRPV)1 and ankyrin 1 (TRPA1) function as cellular sensors for phenomena such as cold and heat and have a prominent role in pain sensation and inflammation. Recent studies demonstrated over dermal immunostaining and or gene expression of TRPV1, TRPV2, TRPV3, and TRPV4 in rosacea. The different TRPVs have an impact on local immune function, vascular regulation, nociception, and epidermal barrier integrity (Wollina 2014).

Table 3 Clinical classification of rosacea. Based on Wilkin J, Dahl M, Detmar M et al. Standard classification of rosacea: report of the National Rosacea Society Expert Committee on the Classification and Staging of Rosacea. J Am Acad Dermatol 2002; 46: 584– 587

Subtype 1 Erythematotelangiectatic	Flushing, central erythema, telangiectasia, stinging, burning, roughness, scaling
Subtype 2Papulopustular	Persistent central facial, erythema, papules, pustules, telangiectasia may be present
Subtype 3Phymatous	Thickened, coarse skin enlarged pores, tissue hyperplasia, nodules
Subtype 4Ocular	Burning, stinging, dryness, foreign-body sensation, eye photosensitivity, telangiectasia of conjunctiva possible
Variants	
Granulomatous rosacea	Reddish-brown nodules in a diffusely red and infiltrated skin

Clinical Aspects

In 2002, the National Rosacea Society Expert Committee developed a classification for standardizing the definition of subtypes, which has been used since then. Four subtypes were defined based on clinical characteristics. Table 3 summarized the classification of rosacea with its subtypes (Wilkin et al. 2002).

Subtype 1, or erythematotelangiectatic rosacea (ETR), begins as a recurring centrofacial erythema which becomes longer lasting and possibly permanent. It may also include edema, stinging and burning sensations, roughness, or scaling. Some triggers as heat, hot liquids, certain foods, alcohol ingestion, sunlight, and stress may induce rosacea flares. Over time teleangiectasias arise on nasal wing and cheek regions (Fig. 12).

The subtype 2, or papulopustular rosacea (PPR), is characterized by persistent erythema and transient pustules and papules in the central facial distribution (Fig. 13).

In subtype 3, or phymatous rosacea, sebacea hyperplasia associated with fibrosis can lead to a thickened skin with irregular surface nodularities and enlargement of affected areas overlying the ears, cheeks, chin (gnathophyma), forehead (metophyma), and nose (rhinophyma).

Subtype 4, or ocular rosacea, is represented by a burning, dry, itchy, and light-sensitive ocular sensation with a bloodshot appearance. Meibomian gland dysfunction presenting as chalazion or chronic staphylococcal infection manifested by hordeolum may be seen and an ophthalmologic approach may be needed. An associated cutaneous rosacea may or may not be present (Wilkin 2002; Wollina 2014; Weinkle et al. 2015).

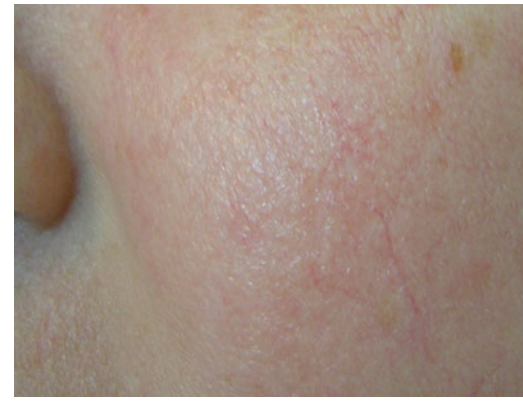

Fig. 12 Erythema and telangiectasia in rosacea

Differential Diagnosis

Other conditions that present facial erythema, papules and pustules, must be distinguished from rosacea, mainly perioral dermatitis, seborrheic dermatitis, and acne. The absence of comedones differentiates rosacea from acne vulgaris. The perioral dermatitis tends to occur in young women and their distribution is more characteristic around the lips, while in rosacea the distribution is more diffuse or predominant in the superior face. In seborrheic dermatitis, polymorphic lesions tend to involve other regions as

retroauricular, around the eyes, scalp, nasolabial folds, sternal and interscapular. Whereas rosacea involves cheeks and nose, but tend to salve the nasolabial folds. Nevertheless, it must be taken in account that rosacea is the most common facial skin disorder overlap with seborrheic dermatitis (SD). A study has demonstrated that 26% of rosacea patients had facial SD and 28% had SD of the scalp (Elewski et al. 2011).

Treatment

Topical Agents

Proper skin care using a mild cleanser and moisturizer promotes skin barrier repair, reduces the burning sensation and tightness of the skin, and can be an adjuvant measure. Changing habits to avoiding trigger factors such as heat and sun exposure are equally important. Topical and oral options are available and relating to the subtype of rosacea, they are summarized in Table 4.

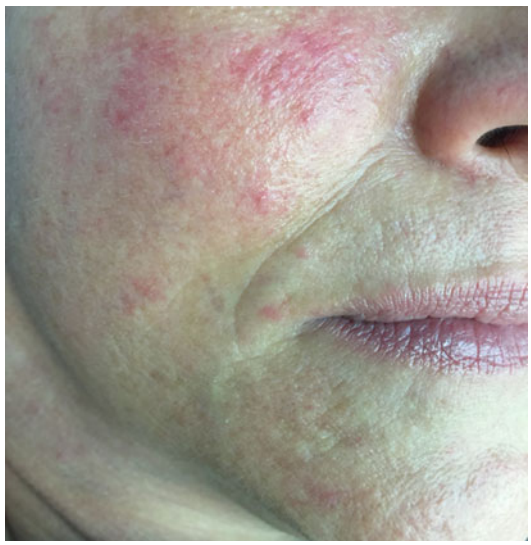

Fig. 13 Erythema, telangiectasia, papules, and pustules

Brimonidine and oxymetazoline are selective α-adrenergic inhibitors that have been used for glaucoma and rhinitis, respectively. Topically applied brimonidine and oxymetazoline are now being used to treat rosacea and shown to be effective in reducing the persistent nontransient facial erythema (Wollina 2014). The therapeutic target of α-agonists are α-receptors present in the smooth muscle layer of the vessel wall of superficial cutaneous blood vessels. A facial application produces a reduction in facial erythema through a vasoconstrictive effect. However, α-agonists have no effect on capillaries and telangiectasias, since they do not contain a smooth muscle layer. Brimonidine tartrate (BT) has been the most extensively studied in clinical trials, with oxymetazoline and xylometazoline published in case reports. A recent year-long study with BT 0.5% gel, applied once a day, established its efficacy and safety, which won FDA approval (Moore et al. 2014). Nevertheless, about 30% of rosacea patients with moderate to severe erythema are resistant to α-adrenergic blockage, which is not yet understood, but it is possible that other neurovascular mechanisms may be involved (Wollina 2014).

A few reports of erythema rebound with 0.5% BT gel showed that some patients may have a greater variability in vascular reactivity, which

Table 4 Treatment of rosacea

Subtype 1 Erythematotelangiectatic		Brimonidine 0.5% gel Pulsed dye laser (PDL), intense pulsed light (IPL)
Subtype 2 Papulopustular	Mild	Azelaic acid 15% gel//Metronidazole 0.75 a 1% Ivermectine
	Severe	Tetracyclines//Doxycycline 40 mg/day Isotretinoin 0.3 mg/kg
Subtype 3 Phymatous	Recent	Isotretinoin
	Established	Surgical tangential excision, electroscalpel, dermabrasion, laser ablation, scissor sculpting, radiofrequency electrosurgery, and wire loop electrosurgery
Subtype 4 Ocular		Doxycycline 40 mg/day//Cyclosporine A 0.05% ocular emulsion Azithromycin1% eye drops

can be inherent and/or related to a great trigger. Patients should be informed of this possibility. Also important is to clarify for patients with papulopustular rosacea that BT operates in erythema but not treat papulopustular lesions (Del Rosso 2014).

Azelaic acid and metronidazole are the topical agents more commonly used in rosacea over the last two decades and both are approved in the USA by the FDA for the treatment of inflammatory lesions of rosacea. Azelaic acid is used as a 15% gel and has anti-inflammatory, antioxidant, and antimicrobial properties that improve markedly the inflammatory lesions of rosacea. It reduces kallikrein-5 activity in affected facial skin, which inhibits the increase in cathelicidin production that has been documented in rosacea-affected skin (Del Rosso 2014). A new formula of foam azelaic acid 15% has demonstrated greater efficacy and tolerability (Draelos et al. 2013).

Metronidazol is used as a 0.75–1% gel, cream, or lotion. The mode of action of topical metronidazole in rosacea is not known, although mechanisms that reduce inflammation in rosacea are believed to be involved. Studies show comparable efficacy of metronidazole and azelaic acid (Weinkle et al. 2015).

Ivermectin, an antiparasitic drug, has been recently approved by the FDA as a 1% cream. In two randomized, double-blind, controlled studies for 12 weeks it proved to be highly effective in inflammatory lesions in PPR patients. This effectiveness could be due to its action against *Demodex folliculorum* and/or to its anti-inflammatory properties (Stein et al. 2014).

Other topical agents are used with recognized benefits despite the insufficient evidence in small clinical reports. These drugs are reserved for difficult cases not responsive to first-line therapy and include tacrolimus, pimecrolimus, erythromycin, clindamycin, azithromycin, retinoids, permethrin, benzoyl peroxide (BP), and BP-clindamycin (Weinkle et al. 2015).

Oral Treatment

The systemic treatment of rosacea has been classically based on oral tetracyclines. Recently their antibiotic effect has been questioned in the rosacea improvement. In this way, a minor doxycycline dosage using 40 mg modified release capsule, given once daily, was proposed. The formulation allows for immediate release of 30 mg with delayed release of 10 mg once ingested. The effectiveness of this antimicrobial subdosage was demonstrated in several studies, probably through anti-inflammatory properties. The advantage of this approach is to keep the anti-inflammatory effect and avoiding bacterial resistance (Del Rosso 2014; Wollina 2014). Modified-release doxycycline 40 mg once daily is now the only systemic agent that is approved by the FDA for the treatment of PPR (Weinkle et al. 2015). As in acne treatment, combination therapy has demonstrated superior improvements than monotherapy. Oral doxycycline or minocycline with azelaic acid or metronidazole has shown substantial improvements in inflammatory lesion counts (Weinkle et al. 2015).

Metronidazole 200 mg taken twice daily and azithromycin 500–1000 mg are second-line options reported to be effective for the treatment of papulopustular rosacea (Weinkle et al. 2015).

Oral isotretinoin has been shown to be very effective in refractory cases of papulopustular rosacea. In a large trial comparing the use of different systemic isotretinoin dosages with both doxycycline and placebo, the optimal effective dose of isotretinoin was found to be 0.3 mg/kg for a minimum duration of 3 months. In the most difficult cases with frequent relapses, continuous "microdose" isotretinoin (0.04–0.11 mg/kg daily) may be an option (Weinkle et al. 2015).

Severe ocular rosacea is best treated with systemic anti-inflammatory drugs, and once-daily low-dose (40 mg) doxycycline is a safe and effective treatment (Wollina 2014). However, new therapies have been tested with success. Cyclosporine A 0.05% ocular emulsion showed effectiveness and superiority over doxycycline (Arman et al. 2015). Other possibly alternative to systemic low-dose tetracyclines is topical azithromycin eye drops (Mantelli et al. 2013).

Other Therapies

Some devices that have been used to treat rosacea, targeted the oxyhemoglobin, the main chromophore in blood vessels, with the aim of controlling the erythema and teleangiectasias on rosacea erythematoteleangiectatic (ETR). These devices include the 595 nm pulsed dye laser (PDL), phosphate (KTP) laser of potassium titanyl, YAG laser of 1064 nm, and noncoherent sources of intense pulsed light (IPL). Once the oxyhemoglobin absorbs the light, the light energy is converted into thermal energy, which diffuses into blood vessels, leading to photocoagulation, mechanical damage, and finally stroke (Mansouri and Goldenberg 2014). In addition, these devices may effectively treat recalcitrant superficial cutaneous vessels that are not responsive to medical therapies in papulopustular rosacea. Diffuse (background) erythema that persists between flares also may improve (Tanghetti et al. 2014). Despite this good performance in ETR, these devices are of little value in other forms of rosacea and so far are considered only as adjuncts in the treatment of rosacea.

Treatment of the Phymatous Changes

In the initial phase isotretinoin may offer some improvement due to its action in sebaceous glands. Once fibroses are established, the phymatous changes are best addressed with surgical and or physical modalities. Approaches for the treatment of rhinophyma include tangential excision, electroscalpel, dermabrasion, laser ablation, scissor sculpting, radiofrequency electrosurgery, and wire loop electrosurgery (Tanghetti et al. 2014).

Take Home Messages

- Although UVA (320–400 nm) and UVB (290–320 nm) seem to be implicated in the photoaging process, UVA is the major contributor because it penetrates deeper into the dermis.
- The first line of defense against photoaging is photoprotection, including seeking shade when outdoors and using sunscreens and protective clothing, and among the 17 UV filters currently approved by the FDA, only two of these filters, avobenzone and zinc oxide ZnO, can absorb long UVA-I radiation.
- Topical retinoids are one of the most important treatments for photoaging. Many different cosmeceuticals products (vitamins, antioxidants hydroxy acids, and plant extracts) can be used isolated or associated with retinoids.
- A genetic predisposition and some exacerbating factors, including pregnancy, the use of hormonal contraceptives, and UV light exposure have been reported in melasma pathogenesis. The more recent observation shows increased vascularity in affected skin as well as the increased expression of vascular endothelial growth factor in the epidermis.
- UV radiation induces melanocyte proliferation, migration, and melanogenesis, but also the visible light (VL) has been implicated in development of melasma, especially in those with darker skin. Opaque sunscreens are more efficacious than chemical sunscreens in protecting against VL.
- Hydroquinone remains the gold standard treatment for epidermal melasma, as monotherapy or combined with tretinoin and topical steroids. Other topical agents (azelaic acid, arbutin, ascorbic acid) may be used as adjuvants. Tranexamic acid, *polypodium leucotomos*, and pycnogenol are systemic drugs recently reported with promising results.
- Acne is a chronic disease, and a maintenance therapy is needed to sustain the remissions.
- Topical retinoids are fundamental. Benzoyl peroxide has a good effect for inflammatory lesions. Topical antibiotics must not be used as monotherapy.
- Isotretinoin is indicated in nodular acne and in refractory cases of severe nonnodular inflammatory acne and/or in patients with a family history of acne and scars.
- Rosacea is a chronic disease and the type and extension of lesions guide the treatment options.

- Topical azelaic acid, sulfacetamide, metronidazole, and, more recently, ivermectine have been described for mild papulopustular cases of rosacea. Severe papulopustular cases require oral antibiotic or isotretinoin. Surgical modalities are the choice for phymas.
- Lasers and intense pulsed light are effective on ETR, but usually adjuvant therapies are necessary.

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Part III

Photoprotection

Photoprotection: Concept, Classification, and Mechanism of Action

Luciana Paula Samorano and Vitor Manoel Silva Reis

Abstract

The harmful effects caused by sunlight on the skin can be divided into acute, such as erythema and pigmentation, and chronic, as photoaging and photocarcinogenesis. Photoprotection refers to a set of measures aimed to reduce exposure to the sun and to prevent the development of actinic damage. There are different forms of photoprotection, including the use of topical, oral, and mechanical photoprotection, and also the education in photoprotection. It is recommended the implementation of actions focused on children, adolescents, adults, and outside workers. The advertisement in the media is very important and helpful. Topic sunscreens may be physical and chemical. The physical filters are inorganic with mineral origin and promote reflection of ultraviolet (UV) radiation. Chemical or organic filters absorb the UV radiation photons, promoting a change in its molecular structure. It is recommended to apply sunscreen on all individual above 6 months old and to use broad-spectrum and water-resistant sunscreens, with a minimum SPF of 30. The association of both oral photoprotection and mechanical sun protection measures, such as clothing, hats, sunglasses, covers for windows, and shadows, seems to bring additional benefit.

Keywords

Photoprotection • Photoaging • Photocarcinogenesis • SPF • *Polypodium leucotomos* • Sunglass • UPF • UV absorbers • Window glass • Automobile glass

Contents

Introduction

There are several effects caused by sunlight on the skin and they can be beneficial or prejudicial. Among other factors, it depends on the intensity, on the wavelength (longer wavelengths penetrate deeper into the skin), and on the skin phototype of

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each individual (Honigsmann 2002; Suh et al. 2007; Schalka et al. 2014).

Regarding their beneficial effects, it is known that exposure to moderate amounts of ultraviolet radiation (UV) promotes wellness, with stress reduction, and improves mental activity. Other benefits include the production of vitamin D3 and aid in the control and treatment of certain skin diseases, such as atopic dermatitis and psoriasis (Corrêa Mde P 2015; Skotarczak et al. 2015).

The harmful effects of UV on the skin can be divided into acute (immediate) and chronic (late) effects. Acute damages are erythema, increased skin temperature, skin thickening, immediate pigmentation, persistent pigmentation, and delayed tanning (Honigsmann 2002; Suh et al. 2007). Chronic adverse effects are photoaging, immunosuppression, and photocarcinogenesis (Svobodova et al. 2006; Katiyar 2007). On the eyes, exposure to UV radiation is associated with the development of pterygium, photokeratitis, climatic droplet keratopathy, and cortical cataract (Yam and Kwok 2014).

The UVB radiation (280–315 nm) comprises 5–10% of the whole UV spectrum of radiation that reaches the earth's surface. It is responsible for erythema and sunburn, pigmentation (delayed tanning – DT), vitamin D3 synthesis, immunosuppression, and carcinogenesis (Honigsmann 2002; Sklar et al. 2013; Skotarczak et al. 2015).

The UVA radiation (315–400 nm) also induces erythema, although to a lesser extent, being the main responsible for stimulating pigmentation. The pigmentation has a biphasic response: immediate pigmentation (IPD – immediate pigment darkening) and persistent pigmentation (PPD – persistent pigment darkening). The IPD occurs within minutes of exposure to UVA and visible light (VL, 400–780 nm) and can last up to 2 h. Sequentially, PPD occurs, peaking in 2 h and lasts up to 24 h. The DT occurs between 3 and 5 days after sun exposure and may persist for several weeks and even months and depends on UVB, as well as on UVA and VL (Honigsmann 2002; Sklar et al. 2013). The UVA also plays an important role in photoaging, in photocarcinogenesis, and in phototoxic and photoallergic reactions (Svobodova et al. 2006; Skotarczak et al. 2015).

Moreover, studies indicate that VL and infrared radiation (IR: 780 to 1 nm) also exert effects on the skin, both acute as erythema and elevation of temperature and chronic, such as photoaging (Sklar et al. 2013; Grether-Beck et al. 2014).

Photoprotection Concept

The photoprotection can be understood as a set of measures aimed to reduce exposure to the sun and to prevent the development of acute and chronic actinic damage. To measure the protection against UVB, we should pay close attention to the sun protection factor (SPF), which should be high. The parameter used to measure the protection against UVA radiation is the PPD (persistent pigment darkening) or PF-UVA (UVA protection factor). In order to protect against VL, it is recommended to use inorganic filters that fully reflect sunlight (Schalka et al. 2014; Skotarczak et al. 2015).

Classification and Mechanisms of Action in Photoprotection

The following subjects are considered as forms of photoprotection: education in photoprotection (photoeducation), topical photoprotection, oral photoprotection, and mechanical photoprotection (covers, glasses, clothes, and accessories) (Schalka et al. 2014; Skotarczak et al. 2015).

Education in Photoprotection

The term photoeducation was proposed in 1988 involving the basics of solar protection, emphasizing the harmful effects of ultraviolet radiation. Later, the use of this term was expanded, encompassing both positive and negative effects of exposure to sunlight (Stengel and Fernandez 2005).

It is recommended the implementation of actions with four major focuses: children and adolescents, adults, outside workers, and actions in the media (Schalka et al. 2014). For children and adolescents, there is evidence that schools have an

important role in photoeducation and that this topic should be incorporated in the curriculum (Buendia-Eisman et al. 2007; Townsend et al. 2011). It is also important to note that the approach should be appropriate for the age range (Stoebner-Delbarre et al. 2005). For the adult population, studies show that, especially for young adults, the approach seems to be most effective when it emphasizes the effects of sunlight on skin aging and on the individual appearance (Stoebner-Delbarre et al. 2005; Hillhouse et al. 2008). In relation to workers who perform outdoor activities, studies point to a higher incidence of precancerous lesions and nonmelanoma skin cancers in this group (Fartasch et al. 2012). The implementation of photoeducation programs for them is an important contribution of their employers (Reeder et al. 2013).

The approach in the lay media also seems to be another important tool for photoeducation. Different resources can be used, such as printout media, television, and radio. This may be even more effective than the advices offered by physicians (Haluza and Cervinka 2013).

Topical Photoprotection

Topical sunscreens are products applied on the skin and contain active ingredients that absorb ultraviolet radiation of 290–400 nm (Quatrano and Dinulos 2013). The benefit of using sunscreens to prevent and treat many skin conditions and diseases is already well established. It is known that the most immediate benefit is the prevention of sunburn. Another important benefit is the prevention of skin cancers, not only nonmelanoma skin cancers but also melanomas (Bens 2014; Skotarczak et al. 2015).

The active ingredients are known as UV filters and are classified into physical and chemical agents. The physical or inorganic filters are from mineral origin and promote reflection of UV to the external part of the tissue. The best known agents are zinc oxide and titanium dioxide, which offer protection against both UVA and UVB radiation. These filters have minimal potential for allergic sensitization and high photostability. However, its reflective property can cause excessive shine and whitish aspect on the skin, limiting its use due to a poor cosmetic acceptability. When it is used in its micronized form, the whitish appearance of the skin is reduced, and it can permeate the stratum corneum and act, in addition to reflection, through diffraction and scattering (Patel et al. 1992; Schalka et al. 2014).

Chemical or organic filters absorb the photons of UV radiation, promoting a change in its molecular structure. The active ingredients approved for use are different when comparing different countries such as the USA, Brazil, and Australia (Quatrano and Dinulos 2013; Schalka et al. 2014). The majority absorbs the UVB radiation spectrum, such as para-aminobenzoic acid (PABA), camphor derivatives (such as Mexoryl SD and Mexoryl SL), and derivatives as p-methoxycinnamate acid (e.g., Parsol MCX). Some of them absorb UVA, including derivatives of dibenzoylmethane (avobenzone), derived from benzidileno, camphor, and phenylbenzimidazole sulfonic acid. Some absorb both UVA and UVB (broad-spectrum filters), such as benzophenones and phenylbenzotriazole sulfonic acids (Tinosorb M, Tinosorb S, Mexoryl XL). These filters, when compared to the physical ones, present greater potential for sensitization and lower photostability (Patel et al. 1992; Schalka et al. 2014). In general, marketed sunscreens have physical and chemical filters combined in its composition.

One of the measures to evaluate the effectiveness of a sunscreen is the sun protection factor (SPF), which quantifies the protection against solar erythema (sunburn), taking into account the minimal erythema dose (MED). As UVB radiation is about 1000 times more erythematogenic than UVA radiation, SPF is primarily a measure of protection against UVB (Palm and O'donoghue 2007; Quatrano and Dinulos 2013). The SPF is calculated by the following formula: SPF = MED (protected skin)/MED (unprotected skin), being the MED of the protected skin evaluated under the use of sunscreen in the amount of 2 mg/cm^2. The SPF value is not related to the duration of exposure to UV radiation but the amount of UV radiation able to produce erythema on the skin

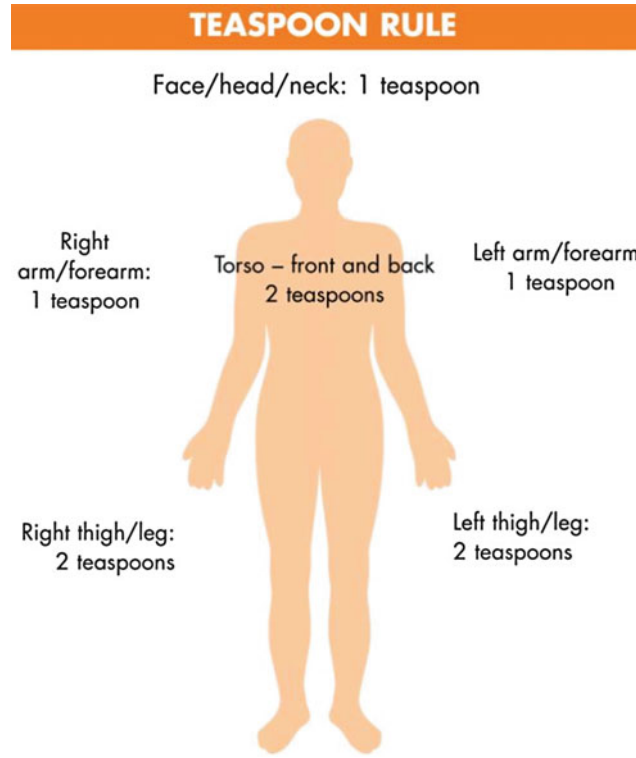

Fig. 1 Ideal amount of sunscreen to be applied on the skin: the teaspoon rule (Adapted from Isedeh et al. (2013))

(Quatrano and Dinulos 2013; Skotarczak et al. 2015).

One of the methods used to evaluate the protection against UVA radiation is the persistent pigment darkening (PPD), also known as UVA protection factor (PF-UVA). The PPD assesses the protection against persistent pigmentation, which results exclusively from UVA radiation action (Schalka et al. 2014).

Another important feature of sunscreens is its water resistance capacity, which should also be tested by established techniques (Schalka et al. 2014).

In addition to protection against ultraviolet radiation, there has been interest for active ingredients that can protect against visible light and infrared radiation, but more researches in this field and regulation are necessary (Grether-Beck et al. 2014).

Current recommendations for the use of sunscreens are to apply it in all individual over 6 months of age; to use a broad-spectrum and water-resistant sunscreen, with a minimum SPF of 30; to apply it in all body areas exposed to UV and not protected by clothing; to evenly apply a generous amount, daily and at all times of the year; to apply at least 15 min before exposure; and to reapply every 2 h, especially after immersion in water or excessive sweating (Quatrano and Dinulos 2013; Schalka et al. 2014). Regarding the amount of sunscreen to be used in each body part, the teaspoon rule can be used (Fig. 1) (Isedeh et al. 2013).

Oral Photoprotection

The oral photoprotection consists of using oral active ingredients that have the ability to minimize the damage caused by solar radiation on the skin (Schalka et al. 2014). To date, there is no oral substance that provides adequate photoprotection when used isolated, not associated with topical sunscreens (Skotarczak et al. 2015).

The main ingredients studied are the carotenoids, some vitamins, and plant extracts. The

carotenoids are derived from vitamin A and are responsible for the yellowish, orangish, and reddish color in animals and plants. The main ones are beta-carotene, astaxanthin, lycopene, and retinol, which can be found in carrots, tomatoes, and peppers. The main feature of these substances is their high activity against reactive oxygen species, and their photoprotective properties have been documented (Jansen et al. 2013; Schalka et al. 2014; Skotarczak et al. 2015).

Vitamins C (L-ascorbic acid) and E (tocopherols) are antioxidants that are used orally or topically (Skotarczak et al. 2015). The human body does not synthesize vitamin C naturally, and, therefore, its dietary intake is required. The main natural sources are fresh fruits and vegetables, such as citrus fruits, currants, rose hips, guava, chili pepper, and salsa (Schagen et al. 2012). Many studies have described the use of topical vitamin C associated with sunscreen, but there is still little evidence of the benefits obtained with this association (Wang et al. 2011; Schalka et al. 2014).

α-Tocopherol is the most active compound and source of vitamin E which have good action as a free radical inhibitor. The main sources of vitamin E are some meats and vegetable oils such as sunflower oil, safflower oil and safflower seed, wheat germ oil, and corn oil (Schagen et al. 2012; Skotarczak et al. 2015). The topical use of vitamin E seems to bring benefit in reducing erythema, sunburn cells, skin damage induced by UVB radiation, and photocarcinogenesis (Eberlein-Konig and Ring 2005; Schalka et al. 2014).

Regarding oral administration of these vitamins, the use of vitamin C showed no photoprotection even in high doses. But the use of vitamin E in high doses appears to mitigate the effects of UVB radiation on the skin. Some studies have shown also that the combination of vitamins C and E orally has more photoprotective effect, compared to monotherapy (Eberlein-Konig and Ring 2005; Placzek et al. 2005). However, more research is needed.

Various plant extracts appear to have antioxidant activity and photoprotective effect. Polyphenols are organic compounds of the phenol group in which at least two hydroxyl groups are attached to an aromatic ring. Depending on the number of phenolic rings and how they are interconnected, polyphenols can be divided into different groups, such as flavonoids, stilbenes (resveratrol), lignans (linseed), and phenolic acids. They are mainly found in fruit (grapes, citrus fruits), fruit juices, coffee, green tea, red wine, vegetables, greenery, cereals, and chocolate. Studies have demonstrated their potential role in photoprotection and in prevention of photocarcinogenesis (Fernandez-Garcia 2014).

Pycnogenol, extracted from pine bark, is another substance with potential photoprotective effects, having the flavonoids as its main ingredient. It appears to have anti-inflammatory, antioxidant, and anticarcinogenic properties (Sime and Reeve 2004).

Also, the *Polypodium leucotomos* stands out, a botanical extract derived from a fern, native of tropical and subtropical regions of the Americas. This extract contains phenolic derivatives such as caffeic acid, ferulic acid and vanillic acid. It acts either topically or by oral prescription reducing the free radicals. They have the ability to inhibit the formation of sunburn cells and the formation of thymidine dimers (Gonzalez and Pathak 1996; Bhatia 2015). Some studies have also shown their benefit when combined with phototherapy with psoralens. It seems that it helps the reduction in erythema, burning, and pigmentation induced by UV radiation (Gonzalez et al. 1997; Middelkamp-Hup et al. 2004).

Mechanical Photoprotection

The term mechanical photoprotection means the use of measures that offer physical or mechanical barrier to sunlight, reducing the incidence of the radiation and its effects on the skin. They include the use of clothing, hats, sunglasses, natural or artificial coverings, and glass (Schalka et al. 2014).

The photoprotection by using clothing and hats offers uniformity and continuity of protection throughout the day and should be considered first-line choice for UVA and especially UVB protection (Palm and O'donoghue 2007). The

clothes block UV radiation in varying degrees, depending on the fabric with which they are made and factors related to its use. The UV protection factor (UPF) was developed as an analogue of sun protection factor to measure the level of UV protection promoted by the fabrics. It is defined as the average of effective UV irradiance of the unprotected skin upon the average of effective UV irradiance of skin protected by fabrics. It can be determined by methods in vitro and in vivo. Fabrics with UPF 15–20 block 93.3–95.8% of the UV radiation and provide good protection; fabrics with UPF 21–35 block 95.9–97.4% and provide very good protection; fabrics with UPF 40 to 50+ block more than 97% of UV radiation and provide excellent protection (Georgouras et al. 1997; Kullavanijaya and Lim 2005; Almutawa and Buabbas 2014).

Several characteristics affect the fabric UPF, such as its composition, weft density, color, wash, adjustment to the body, humidity, and the amount of UV-absorbing agents (UV absorbers) (Table 1) (Edlich et al. 2004; Kullavanijaya and Lim 2005; Almutawa and Buabbas 2014).

The use of hats is an important measure to confer protection to the scalp, especially in bald patients, as well as to help protect the face, ears, and neck. Circular brim hat model is recommended because it also provides protection for the back of the neck. The protection is greater when the plot of the fabric used is tighter. Moreover, UV-absorbing agents can be added to enhance the protection (Edlich et al. 2004; Kullavanijaya and Lim 2005).

Table 1 Main factors which affect the protection provided by fabrics against sunlight (Adapted from Almutawa and Buabbas (2014) and Kullavanijaya and Lim (2005))

Factor	Comment
Type of fabric	Wool and polyester offer high protection; cotton, silk, and linen offer low protection
Weft density	Highest protection in tight and thick weft
Color	Dark-colored fabrics have higher UPF
Wash	UPF increases after washing, due to tissue shrinkage, but decreases with time because the fabric frays apart
Body fit	Less fitting and loose clothes provide greater protection
Humidity	Dry suits provide greater protection
UV-absorbing agents	Adding UV-absorbing agents, such as Tinosorb FD, increases UPF

The use of sunglasses is another important measure in preventing the damage caused by sunlight on the eye structures, in particular the cornea, crystalline lens, and retina (Almutawa and Buabbas 2014; Schalka et al. 2014). The effectiveness of sunglasses against the action of sunlight depends on its size, radiation-absorbing materials incorporated into the lens, and the reflection of posterior surface of the lens. There are three different regulations on the use of sunglasses: one in the USA, one in Australia/New Zealand, and one in Europe. It is usually recommended to use sunglasses that absorb 99–100% of the entire UV spectrum. It should be given preference for lenses that reduce the transmission of blue and violet light, giving greater protection to the retina. It is suggested to avoid too dark sunglass lenses, because they lead to dilation of the pupil and open the eyelid, resulting in increased UV radiation exposure of crystalline lens. The glasses must still protect the area around the eyes (Kullavanijaya and Lim 2005; Tuchinda et al. 2006; Almutawa and Buabbas 2014).

Natural (e.g., vegetation) or artificial shelters are simple and effective measures to reduce direct exposure to UV radiation. They should be used as additional strategy and not as a unique method, since the radiation can scatter into the shadow and by its side. In the case of artificial protections, as cabanas and umbrellas, the type of fabric, the weft density, and the color of them can interfere with the level of sun protection. It should also be considered the position of the subject in the shade and the duration of the exposure (Turnbull and Parisi 2005; Schalka et al. 2014).

The glass is a combination of sand or silica and other components used in construction (windows and glass panels) in automobiles and in glasses. The most common types are ordinary glass (annealed glass), which is flat and broken into large pieces; tempered glass, more resistant to breakage; and laminated glass, made of two or more layers of glass intercalated by a polymeric

material. Besides the type of glass, other characteristics such as color, number of layers, and coatings of glass influence their ability to protect against UV radiation (Duarte et al. 2009; Almutawa and Buabbas 2014; Schalka et al. 2014). Almost all types of glass block almost all of the UVB radiation and reduce the transmission of UVA radiation, which is better blocked by laminated glass (Almutawa et al. 2013; Almutawa and Buabbas 2014; Schalka et al. 2014).

Regarding the colors, studies have shown that green-colored glass completely blocks UVA radiation and the yellow ones almost completely (Duarte et al. 2009). Regarding the thickness, the thickest has additional protective benefit against UVA radiation, although this effect can be discreet (Duarte et al. 2009). Moreover, the greater the distance from the glass to the light emitting source, the lower the irradiance and, hence, lower is the transmission of UV radiation (Kimlin and Parisi 1999).

In cars, the glasses are tempered or laminated. They are usually dyed to improve comfort and to reduce the transmission of VL and infrared (IR) radiation. Although the glass blocks a major part of the radiation, it is believed that there is greater risk of damage by sunlight exposure, as photocarcinogenesis, photoaging, and photodermatosis induction, for the patients who spend long time in the car, mainly in the parts of the body which are closest to the window (Foley et al. 1986; Hampton et al. 2004; Bernstein et al. 2006; Butler and Fosko 2010).

The use of plastic films on car windows (window films) seems to bring an added benefit. With this film there is a complete UVB blocking and an increased UVA blocking (Bernstein et al. 2006; Almutawa et al. 2013; Almutawa and Buabbas 2014).

Take Home Messages

- The sun protection represents an important action to prevent the harmful effects caused by sunlight on the skin.
- It is recommended the implementation of actions in photoeducation directed to children and adolescents, adults, outside workers, as well as actions in the media.
- Sunscreen should be applied to all individuals over 6 months of age. The use of sunscreen with broad spectrum, water resistance, and with minimum SPF of 30 is recommended.
- The association of oral and topical sunscreens seems to bring added benefit.
- Mechanical sun protection measures, such as clothes, hats, sunglasses, natural or artificial coverings, and glass of windows, attenuate the effects of UV radiation on the skin.

Cross-References

- ▶ Chemical and Physical Sunscreens
- ▶ Oral Photoprotection
- ▶ Vitamin D and Photoprotection

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Chemical and Physical Sunscreens

Sergio Schalka, Flávia Naranjo Ravelli, Nicole Perim, and Rossana Vasconcelos

Abstract

Sunscreens are formulations for skin application that contain substances that can absorb, reflect, or disperse solar radiation, reducing its biological effects on the skin (Schalka et al., An Bras Dermatol, 89:1–74, 2014; Schalka and Reis, An Bras Dermatol, 86:507–15, 2011). They are classified in organic or inorganic filters, based on their respective chemical compositions (Schalka et al., An Bras Dermatol, 89:1–74, 2014; Schalka and Reis, An Bras Dermatol, 86:507–15, 2011; Monteiro, Rev Bras Med, 67:5–18, 2010; Shaat, Sunscreens: regulation and commercial development, Taylor and Francis, Boca Raton, pp. 217–239, 2005). The main objective of this chapter is to differentiate the physical and chemical filters, their different galenical presentations, and their effectiveness.

Keywords

Sunscreen • Organic filters • Inorganic filters • Ultraviolet radiation

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Introduction

The reactions caused by sunlight on the skin are many and may be both positive and negative. They depend, among other factors, on radiation intensity and wavelength, as well as on the type of skin of each individual. The appropriate choice and use of sunscreens are decisive in the correct skin protection against UV radiation, avoiding skin cancer, sunburns, and photoaging (Schalka et al. 2014).

Sunscreens

Sunscreens (or topical photoprotectors) are formulations for skin application, in different presentation forms, that contain substances that can absorb, reflect, or disperse solar radiation, reducing its biological effects on the skin (Schalka et al. 2014; Schalka and Reis 2011).

Initially, they were conceived for the purpose of preventing solar burns during outdoor work, leisure, and sports activities. The first formulations appeared in the 1930s and protected only against UVB rays, those mainly responsible for causing erythema and damage to cell DNA. By the 1980s, the role of UVA radiation in photoaging and carcinogenesis, and the importance of formulations containing filters for this radiation, was demonstrated. Thus, a good photoprotector agent is one that protects against both UVA and UVB rays (Schalka et al. 2014; Schalka and Reis 2011; Monteiro 2010; Shaat 2005).

Sunscreen Formulation

UV Filters

Sunscreens contain filters that are agents with the ability to absorb, reflect, or disperse ultraviolet radiation. Their correct use is the main cosmetic approach to protecting from the harmful effects of solar radiation. These substances are commonly classified as "physical filters" or "chemical filters" (Schalka et al. 2014). However, this designation is not adequate, since the action mechanism of sunscreens usually involves physical processes (Schalka and Reis 2011; Monteiro 2010). Thus, the more appropriate classification is organic filters or inorganic filters, based on their respective chemical compositions (Schalka et al. 2014; Schalka and Reis 2011; Monteiro 2010; Shaat 2005).

An inorganic or physical sunscreen acts as a barrier, reflecting the majority of the radiation. Light falling on inorganic particles is redirected, reflected back, or spread out in different ways. The most common examples of this type of filters are zinc oxide and titanium dioxide (Schalka et al. 2014; Schalka and Reis 2011; Monteiro 2010; Shaat 2005). Depending on the size of the particle, the protection can occur not only by means of reflection. When these filters are in a micronized form, they can also act by diffraction and dispersion (Schalka et al. 2014; Schalka and Reis 2011; Monteiro 2010; Shaat 2005).

Inorganic filters have a minimal potential for allergic sensitivity and high photostability, making them especially important for formulating children's products, for daily use and for persons with sensitive skin (Schalka et al. 2014; Schalka and Reis 2011; Monteiro 2010; Shaat 2005). However, their reflective property can cause excessive shine and a whitish aspect, limiting their exclusive use in preparations due to low cosmetic acceptance. A way to solve this problem was the addition of iron oxide pigment to products, providing a makeup base coloration very well accepted by women (Schalka et al. 2014; Schalka and Reis 2011; Monteiro 2010; Shaat 2005).

Sunscreens with inorganic filters have been improved in recent years, through development of micronized forms of titanium dioxide and zinc oxide and by using polymers to encapsulate them. With their micronization, the size of the particles was reduced to 50–90% of the original size, making it possible to develop formulations that become transparent after application, with a consequent improvement in acceptability (Schalka et al. 2014; Schalka and Reis 2011; Monteiro 2010; Shaat 2005).

The size of the particles of inorganic filters is, therefore, a determining factor of their effect. The smaller the particle, the better it covers the skin

and, consequently, the better the reflection; however, refraction is worse. Therefore, reflection and refraction are inversely related. The efficiency of inorganic filters is related to the size and dispersion of their particles (Schalka et al. 2014; Shaat 2005). They can be covered with silicone, silica, aluminum oxide, stearic acid, or aluminum stearate, among others, improving their dispersion, avoiding agglomeration of particles, and altering emulsion rheology. Titanium dioxide, for example, can only be associated with avobenzone when covered with silica and dimethicone. On the other hand, only inorganic filters with particles larger than 200 nm are capable of reflecting in the visible light range (Schalka et al. 2014; Schalka and Reis 2011; Monteiro 2010; Shaat 2005).

Organic or chemical filters are molecules capable of absorbing UV radiation and transforming it into energy radiation harmless to humans. With regard to solubility, they can be hydro or liposoluble (González et al. 2008; Palm and O'Donoghue 2007; Schlossman and Sho 2005). In relation to their action mechanism, the molecules of the absorbing filters contained in sunscreens have numerous double links in their configuration, whether in the benzene ring or the linear chain, allowing many of the electrons found in lower-energy orbits to absorb incident UV radiation and be excited to higher-energy orbits, converting the high-energy radiation and short wavelengths that are highly damaging into low-energy radiations and long wavelengths (González et al. 2008; Palm and O'Donoghue 2007; Schlossman and Sho 2005).

The UV energy absorbed by a molecule is released when it returns to its resting state. Furthermore, its release occurs in the form of fluorescent or phosphorescent light and heat, able to decompose and form photoproducts. Therefore, a sunscreen absorbs harmful energy and transforms it into energy forms that do not damage the skin (González et al. 2008; Palm and O'Donoghue 2007; Schlossman and Sho 2005).

In comparison to inorganic filters, they have higher allergic sensitivity potential and lower photostability, depending on their chemical structure and the combination of components in their formula. More recently, a new generation of organic filters has appeared, with higher photostability and lower potential for skin absorption (reducing the risk of developing an allergic reaction) (Schalka et al. 2014; RIBEIRO, Claudio de Jesus 2006).

However, with the development of new organic and inorganic filters, this classification has become incomplete, since we have organic filters today capable of reflecting UVR and inorganic filters with particles so small (less than 100 nm) that they are able to absorb UVR (Schalka et al. 2014; Shaat 2005).

Organic filters can be divided into UVA filters that protect against UVA radiation, UVB filters that protect against UVB radiation, and broad-spectrum filters that protect against both UVA and UVB radiation (Schalka et al. 2014; Shaat 2005).

Usually, commercial sunscreens use a composition of inorganic and organic filters to expand the photoprotection spectrum (UVA and UVB), exploit synergistic properties, and minimize the adverse effects of a specific component (Schalka et al. 2014; Shaat 2005).

In Brazil, sunscreens are categorized by the National Health Surveillance Agency (ANVISA) as cosmetics, making medical prescription unnecessary for their sale. The same occurs in European countries. However, there is regulation that requires studies to verify safety and efficacy. In the USA, regulatory approval of new filters is slow since sunscreens are considered OTC products (drugs that do not need medical prescription). Many UV filters were developed over the last decade to improve efficacy and safety. However, for regulatory reasons, the list of filters approved for sunscreen development can vary from country to country. There are 16 approved UV filters in the USA, 29 in Australia, 28 in the European Union, and 33 in Brazil. In addition, the concentration of active ingredients allowed to be incorporated in the formulations can also vary (Schalka et al. 2014; Shaat 2005; Agência Nacional de Vigilância Sanitária (ANVISA) 2012). Table 1 shows the components regulated by the FDA.

Filters capable of protecting against visible light act only by reflection, having a whitening effect. As an alternative, different pigments as blocking components of this radiation range are

Table 1 Sunscreen active ingredients currently approved in the FDA monograph

Active ingredients	Maximum concentration (%)	Peak absorption λ (nm)	UV action spectrum
Organic filters			
UVA filters			
Benzophenones			
Oxybenzone (benzophenone-3)	6	288.325	UVB, UVA II
Sulisobenzone (benzophenone-4)	10	366	UVB, UVA II
Dioxybenzone (benzophenone-8)	3	352	UVB, UVA II
Dibenzoylmethanes			
Avobenzone (butyl methoxydibenzoylmethane, Parsol 1789)	3	360	UVA I
Anthralates			
Meradimate (menthyl anthranilate)	5	340	UVA II
Camphors			
Ecamsule * (terephthalylidene dicamphor sulfonic acid, Mexoryl SX)	10	345	UVB, UVA
UVB filters			
Aminobenzoates (PABA derivatives)			
PABA (para-aminobenzoic acid)	15	283	UVB
Padimate-O (octyl dimethyl PABA)	8	311	UVB
Cinnamates			
Cinoxate (2-ethoxyethyl p-methoxycinnamate)	3	289	UVB
Octinoxate (octyl methoxycinnamates [OMC])	7.5	311	UVB
Salicylates			
Octisalate (octyl salicylate)	5	307	UVB
Homosalate (homomenthyl salicylate)	15	306	UVB
Trolamine salicylate (triethanolamine salicylate)	12		UVB
Others			
Octocrylene	10	303	UVB, UVA II
Ensulizole (phenylbenzimidazole sulfonic acid)	4	310	UVB
Inorganic filters			
Titanium dioxide	25		UVB, UVA
Zinc oxide	25		UVB, UVA

used, providing a "base" appearance to the formulation (Schalka et al. 2014; Shaat 2005).

Sunscreens able to protect against infrared radiation do so through addition of ingredients capable of reducing cell or molecular damage caused by this radiation (Schalka et al. 2014; Shaat 2005).

Galenic Formulation

Topical sunscreens can be transmitted in different pharmaceutical forms. Pharmaceutical formulas consist of a main component (substance that provides the desired therapeutic benefit), a vehicle (responsible for incorporating the other components), and excipients such as emollients, solvents, emulsifiers, preservatives, and fragrances, among others (Schalka et al. 2014; Palm and O'Donoghue 2007; Teixeira 2012; Chorilli et al. 2006).

The appropriate choice of vehicle and other components for a sunscreen formulation is as important as the main component itself, contributing to a satisfactory final result, stability, and efficacy of the formula (Schalka et al. 2014; Palm and O'Donoghue 2007; Teixeira 2012; Chorilli et al. 2006).

Excipients are essential in preparing formulations – they must be inert but contribute to the appearance, stability, and safety of sunscreens. Examples of excipients include emulsifiers, preservatives, and fragrances, among others. The use of polymers in formulations can improve spreadability, absorption, and film formation on the skin. In other cases, the use of emulsifiers to incorporate organic filters into the vehicles can interfere with the absorption curve of the main component (Schalka et al. 2014; Palm and O'Donoghue 2007; Teixeira 2012; Chorilli et al. 2006).

The vehicle also does not have pharmacological action, but it is responsible for incorporation of the other components. Its choice influences the stability and efficacy of the formulation, contributing to an effective SPF level. In addition, the physical-chemical composition and state of the vehicle influence the cosmetics, thus determining which type of skin is appropriate for each formulation (Schalka et al. 2014; Palm and O'Donoghue 2007; Teixeira 2012; Chorilli et al. 2006).

The choice of appropriate vehicle should take the treatment objective and characteristics of each patient into consideration and increase the efficacy of the formula and adherence of the sunscreen. There are a number of presentation forms, such as oils, gels, emulsions, mousses, aerosols, sticks, compact powder, and bases (Schalka et al. 2014) (Table 2).

Table 2 Various presentations of sunscreens and their characteristics

Presentation	Skin sensation	Water resistant	Need for reapplication
Cream/lotion (emulsion)	Pleasant	Yes	Less frequent
Mousse	Pleasant	Yes	Less frequent
Oily gel	Oily	Yes	Less frequent
Aqueous gel	Pleasant	No	Frequent
Hydroalcoholic gel	Pleasant	Yes	Less frequent
Gel-cream	Pleasant	Yes	Less frequent
Sticks	Greasy	Yes	Less frequent
Spray/aerosol	Oily	Yes	Less frequent
Oil	Oily	Yes	Less frequent

Adapted source: Teixeira SMMCG 2012

Oils

Oils are single-phase vehicles that can be easily manipulated and quite stable for incorporation of liposoluble components. When applied to the skin, they have good spreadability and are quite water resistant. However, they are limited cosmetically since they are oily, leave an excessive shine on the skin and soil clothing, and are difficult to remove. In addition, the easy application leads to only a fine transparent layer of the product on the skin, achieving reduced SPF values (Schalka et al. 2014; Palm and O'Donoghue 2007; Teixeira 2012; Chorilli et al. 2006).

Gels

A gel is a semisolid preparation formed primarily by polymers dispersed in a liquid medium. The liquid phase, in general, is composed of water or alcohol, while the solid phase is represented by gelling agents. Hydrogels are easily applied and provide a dry and transparent film over the skin; however, they are not water resistant and do not provide high SPF values. Alcohol gels are cosmetically similar to hydrogels, providing higher SPF levels; however, they can cause skin dehydration and should be avoided by people with skin xerosis and sensitive skin. On the other hand, oil gels or gel-creams have characteristics similar to oils and are water resistant. Moreover, they leave a denser film on the skin than do oils, providing stronger photoprotection (Schalka et al. 2014; Palm and O'Donoghue 2007; Teixeira 2012; Chorilli et al. 2006).

Emulsions

Emulsions are dispersions of two immiscible phases (aqueous and oily), which form a homogeneous and stable system through the action of an emulsifier. Emulsions can be classified in different ways, for example, taking the proportion between the aqueous and oily phases into account. In water-in-oil (W/O) emulsions, the continuous phase of the emulsion is the oil and the disperse phase the water, resulting in more oily formulations that leave a

shine on the skin and are more water resistant. The oil/water (O/W) emulsions are less greasy, dry quickly, and are easier to remove with water. This is a vehicle with versatile properties, cosmetically pleasing and compatible with the incorporation of lipo- and water-soluble substances, making it one of the most prescribed pharmaceutical forms. They can be divided into liquid emulsions (fluid or lotion emulsions) or pasty emulsions (creams) depending on their physical aspect (Schalka et al. 2014; Palm and O'Donoghue 2007; Teixeira 2012; Chorilli et al. 2006).

Silicone-in-water emulsions should also be highlighted. Silicones allow incorporation of large content in the aqueous internal phase and replace oils with the advantage of having greater chemical inertia, and when well structured, the oily characteristic disappears (Schalka et al. 2014; Palm and O'Donoghue 2007; Teixeira 2012; Chorilli et al. 2006).

Gel-Cream

Gel-cream is an emulsion that contains a high percentage of aqueous phase and low oil content, stabilized by hydrophilic colloids. They are cosmetically pleasing, combining the sensory effect of gels with the emollience of emulsions. It is a vehicle commonly used in tropical countries and appropriate for oily skin since it allows incorporation of oil-sequestering agents (Schalka et al. 2014; Palm and O'Donoghue 2007; Teixeira 2012; Chorilli et al. 2006).

Mousses

A mousse is a fluid emulsion, conditioned in a special packaging with a valve that when squeezed forms an elegant foam, easily spreadable (Schalka et al. 2014; Palm and O'Donoghue 2007; Teixeira 2012; Chorilli et al. 2006).

Aerosols

Aerosols are colloidal dispersions of a liquid in a gas. They provide a continuous and homogeneous flow, are easy to apply, and provide an interesting presentation for the scalp, hairy areas, hard-to-reach areas, or large surfaces. Aerosols in general are oily and easily spread over the skin, leaving a fine but oily layer. Formulas containing silicone are more accepted cosmetically, however questionable in relation to the uniformity of coverage (Schalka et al. 2014; Palm and O'Donoghue 2007; Teixeira 2012; Chorilli et al. 2006).

Sticks

Sticks are solid forms made up of waxes and oils, very water resistant and ideal for small areas such as the lips, nose, and cheeks. Liposoluble inorganic and/or organic sunscreens can be incorporated, and they are quite effective; however, they can leave an oily appearance and are expensive (Schalka et al. 2014; Palm and O'Donoghue 2007; Teixeira 2012; Chorilli et al. 2006).

Powders and Bases

These are cosmetic products which incorporate sunscreens. They have a very useful makeup effect, ensuring a uniform color to the skin, reducing shine, and providing photoprotection. Organic and inorganic filters can be added to compact powders and bases, while only inorganic filters are generally incorporated in powders (Schalka et al. 2014; Palm and O'Donoghue 2007; Teixeira 2012; Chorilli et al. 2006).

Other Ingredients

Recently, different components with antioxidant action have been incorporated in sunscreen formulations, with biological action to reverse oxidative damage caused by radiation. These components have no direct action on incident radiation, like the ultraviolet filters mentioned above, but they interfere in a secondary manner, at the cellular or molecular level, neutralizing reactive oxygen species (ROS) (Schalka et al. 2014; Gonzalez et al. 1996; Kenneth and Palefsky 2005).

In addition to antioxidants, new components have been proposed, with biological actions that go beyond antioxidant action. Two examples of these components are *Polypodium leucotomos* extract, with antioxidant action and a modulator of the immunological response resulting from

Table 3 Main antioxidant components used in sunscreen formulations

Antioxidant component	Source
Vitamin C	Fruits, vegetables
Vitamin E	Vegetable oil, seeds
Green tea polyphenols	Green tea fractions
Soy isoflavones	Soybeans, Ginkgo biloba
Caffeic acid and Ferulic acid	Coffee beans, propolis
Selenium	Corn, soybeans, wheat
Pycnogenol	Pine bark extract
Resveratrol	Grape skin and seeds
Polypodium leucotomos	Extract from a tropical fern variety

solar radiation, and *Photolyase*, with photo-chemopreventive action, repairing DNA damaged by the effect of radiation (Schalka et al. 2014; Gonzalez et al. 1996; Kenneth and Palefsky 2005).

There are also components with the ability to protect mitochondrial DNA, particularly against the effects of infrared radiation, as in the case of *Artemia salina* plankton extract (Schalka et al. 2014; Gonzalez et al. 1996; Kenneth and Palefsky 2005).

Table 3 shows some of the main antioxidant components used in sunscreen formulations.

Assessment of Sunscreen Efficacy

The first method described, and still considered a reference for assessment of the photoprotection efficacy of sunscreens, is the sun protection factor (SPF) that is based on evaluation of the minimum erythematous dose between the skin protected by a sunscreen (application of 2 mg/cm^2) and unprotected skin, conducted with a group of volunteers exposed to radiation-emitting equipment with a spectrum similar to sunlight. The SPF is a measurement capable of essentially quantifying protection against UVB radiation, with little interference on the evaluation of protection against UVA (Schalka et al. 2014; Diffey and Kochevar 2007; DeBuys et al. 2000; Lui and Anderson 2007; Schalka et al. 2009).

For quantification of UVA protection, Moyal et al. (2000) presented a method called "persistent pigment darkening" (PPD) for evaluation of protection in the UVA range. This method, today called UVA protection factor (UVA-PF), is considered the most adequate method for determining protection in the UVA range and can be conducted in vivo or through spectrophotometry (in vitro). The target biological event of the UVA-PF method is immediate pigmentation resulting from oxidation of the melanin formed, an event resulting from UVA radiation (Moyal et al. 2000a; Moyal et al. 2000b; Yaar 2007).

For a sunscreen to be qualified to provide balanced UVA/UVB protection, it must have a minimum UVA-PF of 1/3 of the SPF and a critical wavelength (spectrophotometry method) greater than 370 nm (Schalka et al. 2014; Moyal et al. 2000a; Moyal et al. 2000b; Yaar 2007).

In addition to ultraviolet radiation, waves of greater length, like infrared radiation and primarily visible light, are capable of triggering photobiological phenomena on the skin. In particular, the action of visible light in triggering pigmentation has been demonstrated (Mahmoud 2008; Rhodes and Lim 2007).

So far, there are no substances capable of absorbing visible light, and protection against it can only be provided by particles (inorganic filters) or pigments capable of reflecting or dispersing visible light by means of optical mechanisms. Reliable methods capable of quantifying protection against visible light have not yet been found (Mahmoud 2008; Rhodes and Lim 2007).

Studies also show the effect of type A infrared radiation (760–1,000 nm) on the production of oxygen reactive species through mitochondrial action. Antioxidant components can reduce the production of these reactive species, demonstrating, therefore, antioxidant action against infrared radiation. There are methods capable of measuring the antioxidant efficacy in cellular cultures when exposed to type A

infrared radiation (Mahmoud 2008; Rhodes and Lim 2007).

Take-Home Messages

- Sunscreens contain substances that can absorb, reflect, or disperse solar radiation, reducing its biological effects on the skin.
- Sunscreens are commonly classified as "physical filters" or "chemical filters." However, this designation is not adequate, and the more appropriate classification is organic or inorganic filters.
- An inorganic sunscreen acts as a barrier, reflecting the majority of the radiation. The most common examples of this type of filters are zinc oxide and titanium dioxide.
- Organic filters are molecules capable of absorbing UV radiation and transforming it into energy radiation harmless to humans.
- Topical sunscreens can be transmitted in different pharmaceutical forms (gels, emulsions, gel-cream, spray, powder, among others), and the appropriate choice of the product contributes to the efficacy of the formula.
- Antioxidants and modulators of the skin immunological response have been incorporated in sunscreen formulations.
- The efficacy of sunscreens depends on the SPF, the UVA-PF, the ratio UVA/UVB, and the critical wavelength.
- Filters capable of protecting against visible light have a whitening and unpleasant effect. As an alternative, different pigments are used providing a "makeup base" appearance to the formulation.
- Sunscreens able to protect against infrared radiation do so through addition of ingredients capable of reducing cell or molecular damage caused by this radiation.

Cross-References

- ▶ Oral Photoprotection
- ▶ Photoprotection: Concept, Classification, and Mechanism of Action
- ▶ Vitamin D and Photoprotection

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Oral Photoprotection

Flávia Alvim Sant'Anna Addor, Humberto Ponzio, and Flávia Naranjo Ravelli

Abstract

Better understanding of molecular damage caused by solar radiation has led to the growing study of molecules with antioxidant and anti-inflammatory activity against photodamage. Oral use of these substances is considered an important coadjutant in photoprotection strategy, due to two general mechanisms: prevention and mitigation of photodamage. Coming from nutrients, such as vitamins and functional foods, or herbal extracts, and, more recently, probiotics, molecules with oral photoprotection action have antioxidant action, protecting especially from damage to DNA and protein and lipid structures, but they can also prevent or mitigate UV-induced inflammation, acting on the epidermis and dermis. An increase in the minimal erythema dose has also been shown with some associations of nutrients.

Although the level of evidence varies considerably between the molecules studied and described, the most-used active constituents with proven safety and efficacy under systemic use are presented below.

These molecules act most often in association, providing a synergistic effect that also allows reduction of their respective concentrations and, consequently, greater tolerability for use.

Keywords

Photoprotection • Antioxidants • Vitamins • Photodermatosis • Pycnogenol • Polypodium leucotomos • Ultraviolet

Contents

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Introduction

Studies have shown that the oxidative mechanisms resulting from solar radiation are related to photocarcinogenesis, photoaging, and much of the etiopathogeny of photodermatoses (Haywood et al. 2003).

The use of topical sunscreens as the sole means of photoprotection has not proven to be a completely effective measure to control generation of reactive oxygen species (ROS), nor protection against the endogenous mechanisms of their neutralization. Measures to protect against UVA and UVB do not necessarily correspond to protection against oxidative damage (Gilaberte and González 2010a).

Sunscreens are not able to block low-energy photons that do not cause clinical erythema, but can induce immunosuppression and DNA mutations in epidermal and dermal cells. These reactions generate free radicals that increase the alterations, such as cellular apoptosis and an increase in expression of metalloproteinases (Bernerd et al. 2000). At the same time, more recent research has shown that other solar spectrum bands, such as visible and infrared radiation, are also capable of producing oxidation, but there is still no evidence of a clinical correlation as there is for ultraviolet radiation (Gonzalez et al. 2011).

The use of substances with antioxidant or even anti-inflammatory action is being studied as an alternative to reduce the molecular damage that sunscreens are incapable of neutralizing. Although it has commonly been called oral photoprotection, its mechanism is much more based on mitigating oxidative and inflammatory phenomena rather than preventing them, although there are some substances or associations that are known to increase the skin's defenses.

Basic Concepts

The mechanisms of photodamage can be direct (direct damage to DNA or the cell itself, with necrosis) or indirect (by oxidative mechanisms, leading to mutations and causing inflammation) (Farage et al. 2008).

The skin uses a wide range of endogenous or exogenous antioxidants coming from the diet; some of the oxidative damage is neutralized by these mechanisms. The need for greater support results from two situations: when the intensity of the damage exceeds defensive capacity or when the mechanisms are in decline or lacking, for example, due to chronological aging itself (Shindo et al. 1994).

The focus of sunscreens, as well as all external photoprotection measures, is to reflect, absorb, or disperse solar radiation, but it has been shown that sunscreens are not able to completely impede interaction of the radiation with the skin, causing photodamage, and their efficacy is related to adequate and frequent use. Therefore, oral use of antioxidant and/or anti-inflammatory substances complements topical photoprotection.

Obviously they cannot be used as substitutes for sunscreens used topically, since they are not able to reflect, absorb, or disperse radiation, but they can complement action to prevent photodamage, both due to photoaging and photocarcinogenesis and photodermatosis (Krutmann 2000).

Multiple agents demonstrate antioxidant action against photodamage, but information on their effects still varies enormously between substances. In vitro demonstration is important to show the mechanism in action, but it does not necessarily mean that its oral use ensures the same effects (Zattra et al. 2009). Since the studies are clinical, or at least in an animal model, they are essential for understanding the real effect, providing an adequate indication with realistic expectations.

In the current scenario, oral photoprotection is a valuable coadjutant, since, in addition to having a good margin of security, it supports the effect of other photoprotection measures and may make a difference in treatment of chronic pathologies related to sunlight, such as melasma and polymorphic light eruption (Emanuel and Scheinfeld 2007).

In photoaging, where solar radiation in its ultraviolet, visible, and infrared spectrums leads to oxidative phenomena as a common denominator, the use of oral antioxidants is an important resource as a coadjutant, both in prevention and in actual treatment of its signs (Schalka et al. 2014).

Background

The relationship between nutrition and health and skin appearance is a recurring subject in the history of medicine (Peirce 1945). With the discovery of free radicals in the 1950s and their relationship with damage to DNA and other molecules, such as cellular proteins and lipids (Harman 1962), the mechanism of physiological antioxidant systems was widely studied, as were exogenous substances with this behavior, particularly nutrients (Johnson 1966; Glavind and Christensen 1969). However, the behavior of oxidative phenomena causing photodamage gained attention starting in the 1990s, with demonstration of the damaging mechanisms of ultraviolet radiation A (Taylor et al. 1990; Bissett et al. 1990).

Carotenoids were the first to be documented, but soon the value of vitamins, molecules coming from nutrients, and herbal extracts was perceived (Bartley and Scolnik 1995; Werninghaus et al. 1994; Landrum and Bone 2001; Gonzalez and Pathak 1996; Lambert et al. 2005) and, more recently, probiotics (Guéniche et al. 2009).

Classification

There are a variety of substances alleged to have photoprotective action when ingested orally; they can be classified in the following manner:

1. Antioxidant action:
   a. Hydroxycinnamic acids:
      i. Caffeic acid
      ii. Ferulic acid
   b. Vitamins
      i. Carotenoids
      ii. Ascorbic acid
      iii. Tocopherol
   c. Polyphenols:
      i. Flavonoids
         - Anthocyanidins
      ii. Green tea extract (epigallocatechin gallate)
      iii. Resveratrol
   d. Pycnogenol® (French Maritime pinus extract)
   e. Fernblock® (Polypodium leucotomos extract)
   f. Caffeine
   g. Coenzyme Q10
2. Anti-inflammatories
   a. COX-2 inhibitors
   b. Polyunsaturated fatty acids
3. Antimalarials
4. Probiotics

Main Active Constituents

Antioxidants

Hydroxycinnamic Acids

They have the ability to prevent UVB-induced erythema and prevent oxidative damage, both in vitro and in vivo (Saija et al. 2000).

Vitamins

Carotenoids

In oral photoprotection, they consist of carotene, lycopene, and lutein molecules; their main property is their ability to neutralize oxygen. The use of carotenoids in combination exhibits a synergistic effect (Stahl and Sies 2002).

Beta-carotene demonstrates various mechanisms involved in reducing photodamage, inhibiting degradation of the extracellular matrix, and promoting differentiation of keratinocytes, as well as increasing the tanning-associated protease-activated receptor 2. A clinical study showed a reduction in risk of melanoma 3857. However, as a systemic photoprotector, it did not show significant action in monotherapy (Cesarini et al. 2003).

Astaxanthin and lutein were shown to have protective action against UVA damage in in vitro studies, but lutein is also capable of reducing metalloproteinase activity (MMPs) and

degradation of elastin in fibroblasts radiated by UV, as well as filtering blue light. However, there is still no clinical proof of these effects in monotherapy (Palombo et al. 2007).

Lycopene, the main carotenoid in tomatoes, is a potent inhibitor of singlet oxygen, significantly inhibiting erythema (Stahl et al. 2006).

Ascorbic Acid

Vitamin C is the water-soluble antioxidant most corroborated in the literature, but its oral use as a photoprotector should occur in association with tocopherol (Chandra et al. 2003).

Tocopherol

Vitamin E's antioxidant effect against UV-induced damage has been largely proven. Inhibition of lipid peroxidation has been proven; however its effect is moderate when used alone; its effect is improved when associated with carotenoids and other substances, such as trace elements and vitamin C itself, which is capable of recycling it (Eberlein-Konig and Ring 2005).

Polyphenols

These consist of flavonoids and phenolic acids, having potent antioxidant action, as well as evidence of anti-inflammatory activity. Flavonoids are basically isoflavones, with the most studied being genistein, capable of inhibiting UV-induced damage; in this group silymarin, equol, daidzein, quercetin, and apigenin are studied for their antioxidant properties. Among the flavonoids, in the anthocyanin group, delphinidin is the most studied since it exhibits a potent antioxidant action and shows anti-inflammatory action (Kuskoski et al. 2004). Epigallocatechin (green tea) is capable of inhibiting, in addition to lipid peroxidation, immunosuppression, by inhibiting the depletion of Langerhans cells (Lu et al. 2001). Resveratrol, found especially in grapes, exhibits an antioxidant effect against UVB-induced damage, reducing the generation of ROS and inflammation (Afaq et al. 2003).

Pycnogenol® (French Maritime Pinus Extract)

Pycnogenol is an extract of French maritime pinus extract (*Pinus pinaster*). There is evidence of its antioxidant and anti-inflammatory action, and it also demonstrates antineoplastic activity. Pycnogenol prevents UV-induced erythema, as well as long-term effects, such as immunosuppression and neoplastic proliferation (Bito et al. 2000).

Fernblock® (Polypodium Leucotomos Extract)

Fernblock is the extract obtained from this species of fern. It demonstrates the ability to inhibit UVA- and UVB-induced erythema. Its antioxidant and immunomodulator action, acting on the inflammatory cytokines, has been demonstrated, as well as its ability to inhibit UV-induced depletion of Langerhans cells. Its protecting effect has been demonstrated in clinical studies of patients undergoing phototherapy, reducing the expression of metalloproteinases (Brieva et al. 2002; Middelkamp-Hup et al. 2004).

Caffeine

Caffeine is capable of inhibiting UVB-induced apoptosis of keratinocytes, suggesting a preventive effect in photo carcinogenesis (Kerzendorfer and O'Driscoll 2009).

Coenzyme Q10

Coenzyme Q10 acts on cellular respiration at the mitochondrial level, also protecting this organelle against photodamage, and is also capable of recycling tocopherol (Farris 2007; Dong et al. 2007).

Anti-inflammatories

COX-2 Inhibitors

Cyclooxigenase-2, an enzyme linked to neoplastic cell proliferation, is inhibited by celecoxib, which has been shown to inhibit inflammation and production of UV-induced PGE2 (Fischer et al. 1999). There have also been reports of use of acetylsalicylic acid, indomethacin, and ibuprofen, when used shortly before or immediately after irradiation (Edwards et al. 1982).

Polyunsaturated Fatty Acids

Of this group of lipids, omega 3 fatty acids, particularly those derived from fish, have the greatest anti-inflammatory action, but they can also be of vegetable origin, such as flaxseed. High doses in monotherapy demonstrate a reduction in UV-induced erythema and inflammation, due to the effect on modulation of anti-inflammatory prostaglandin synthesis (Moison and Beijersbergen Van Henegouwen 2001).

Antimalarials

Some antimalarials, in particular, chloroquine, have an anti-inflammatory effect, inhibiting the synthesis of interleukin 1, being used therefore in some photodermatoses like lupus. However, the side effects of this group of drugs do not justify their use purely as systemic photoprotectors (Rainsford et al. 2015).

Probiotics

Based on the systemic immunomodulator mechanism that the use of probiotics provides, a clinical study has shown a better defense response to UV damage after their use. Although this mechanism is promising, there is still little evidence of the action mechanism of these microorganisms (Guéniche et al. 2009).

Indications and Contraindications

The use of nutrients with systemic photoprotective action is indicated for prevention of solar damage and as a support for treatment of dermatoses that worsens with sun exposure. There are few studies with doses above the RDI, with varied doses and results (Addor et al. 2013; Cho et al. 2007).

- With regard to the extracts:
  - *Pinus pinaster*: its use lies in its antioxidant action and in melanogenesis, indicated for patients with melasma (Ni et al. 2002).
  - *Polypodium leucotomos*: it is mainly indicated in Brazil for polymorphic light eruption, but there are several studies on other photodermatoses due to its antioxidant and immunomodulator effect, such as for melasma, vitiligo, and other photodermatoses, such as solar urticaria and lupus (Brieva et al. 2002).
  - Anti-inflammatories: their use as systemic photoprotectors is not routine, being indicated occasionally for treatment of severe damage, such as solar erythema.
- Use and doses:
  - For nutrients, the RDI is the safest and most adequate, normally in commercial associations, according to manufacturer recommendations (Lima et al. 2012).
    - *Pinus pinaster*: 50–75 mg per day
    - *Polypodium leucotomos*: 750 mg–1 g per day

These doses, as well as associations, may be taken.

Side Effects and Their Management

In systemic photoprotection, a large number of the active constituents are of nutritional origin; however, when used in physiological doses (in RDI or recommended daily intake) generally in associations, there are no contraindications nor risks of drug interaction. Care in administration should be observed, particularly in nephropathies and hepatopathies, for the excretion and metabolization, respectively (Addor et al. 2013; Cornelli 2009).

Pinus pinaster: nothing specific, no drug interaction.
Polypodium leucotomos: nothing specific, no drug interactions are described.
Anti-inflammatories: their contraindications are those inherent to these drugs and not discussed in this chapter.

Conclusion

Solar radiation can cause skin damage, triggering skin cancer, photoaging, and photodermatoses. Oral photoprotection has been used to minimize

this damage through antioxidant and anti-inflammatory mechanisms.

Take-Home Messages

- Systemic photoprotection is important as a coadjutant in any dermatosis that is triggered or aggravated by solar radiation.
- The use of substances with antioxidant or even anti-inflammatory action is being studied as an alternative to reduce the molecular damage that sunscreens are incapable of neutralizing.
- Oral photoprotectors cannot be used as substitutes for sunscreens used topically, since they are not able to reflect, absorb, or disperse radiation, but they can complement action to prevent photodamage.
- Multiple agents demonstrate antioxidant action against photodamage, but information on their effects still varies enormously between substances.
- The association of ingredients has been shown to have a more effective photoprotective action and should be proven.

Cross-References

- ▶ Approach in Photodamaged Skin, Melasma, Acne, and Rosacea
- ▶ Chemical and Physical Sunscreens
- ▶ Photoprotection: Concept, Classification, and Mechanism of Action

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Vitamin D and Photoprotection

Marcus Maia and Carolina Marçon

Abstract

Vitamin D, which has a well-established key role in bone health, is currently at the forefront of discussions in the dermatology field due to recent evidence of its role in extra-skeletal health. Vitamin D is obtained mainly through sunlight, and many factors can influence the conversion of vitamin D to its active variant in the skin, including environmental factors such as geographic location, seasonality, and atmospheric characteristics and individual factors such as age, skin type, and lifestyle, among others. Debate concerning the effects of solar protection on cutaneous synthesis of vitamin D has emerged in recent years. A recent literature review emphasized that adequate levels of vitamin D are needed to prevent osteoporosis, falls, and fractures in the elderly population. Emerging data also point to its role in cardiovascular diseases, autoimmunity, and some types of cancer. The normal and regular use of sunscreen for adults has not been shown to decrease the cutaneous synthesis of vitamin D. The daily recommendations for vitamin D intake, published in 2010, were based on the skeletal effects of this vitamin. Oral ingestion through fortified food or vitamin D supplementation is recommended for patients who are not usually exposed to the sun in order to maintain adequate serum levels. Patients should not be discouraged from using sunscreen due to its well-established photoprotective and preventive effects. It is important that we know all of the factors involved in the production of vitamin D, so we can analyze each patient individually and clearly determine the ideal conduct for each case, without prejudice or harm.

Keywords

Skin cancer • Photoprotection • Vitamin D • Sunburn • Photoprotectors • Skin diseases • Ultraviolet rays

Contents

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Introduction

The beneficial and harmful effects of human exposure to solar ultraviolet (UV) radiation (UV-R) are issues that arouse great interest not only in doctors and scientists but also the general public and media. In Brazil, discussions regarding the benefits of sun exposure for vitamin D synthesis are currently focused on the significant concern about the already high and growing number of new cases of skin cancer diagnosed every year in Brazil and worldwide. However, a significant part of these discussions lacks scientific backing or is based on studies conducted in Europe and the USA, where the quantities of UV-R reaching the skin's surface, habits relating to sun exposure, and the characteristics of the population are significantly different to those observed in Brazil (Corrêa 2015).

Given the damaging effects of solar exposure, one of the main controversies is related to the time required for beneficial effects to occur without being damaging to a person's health, i.e., how long it takes to synthesize a significant amount of vitamin D without the skin being damaged.

Humans obtain vitamin D from sunlight, their diet (especially fish and fortified milk), and supplements (Table 1). It acts as a hormone and its regulation involves parathyroid hormone (PTH), calcium, and phosphorus, which has many important physiological consequences, especially regarding skeletal health. Vitamin D receptors and enzymes capable of converting 25-hydroxyvitamin D (25(OH)D) into its circulating active form, 1,25 dihydroxyvitamin D (1,25(OH)D), were found to be evident in most cells in the body, leading to a multitude of new insights into their function (Holick 2007). In addition to a protective role against bone fractures, rickets, osteomalacia, and osteoporosis, vitamin D is now proposed to be responsible for reduction of a range of chronic diseases, including internal cancers, cardiovascular diseases, autoimmune diseases, metabolic disorders, and mental illness (Grant 2002; Holick 2004). Its importance in immunology and infectious diseases has been demonstrated by associating its deficiency with, for example, increased rates of tuberculosis (Wilkinson et al. 2000; Liu et al. 2006). One study reported that the incidence of influenza in winter is reduced when the appropriate vitamin D status is maintained (Aloia and Li-Ng 2007).

Table 1 Vitamin D and diet

Food	Vitamin D, IU per serving
Cod liver oil—1 tbsp	1360
Cooked red salmon—93 g	447
Cooked mackerel—93 g	388
Drained canned tuna in water—93 g	154
Orange juice fortified with vitamin D—1 cup	137 (amount varies by product)
Milk fortified with vitamin D—1 cup (skim, skim semi, full)	115–124
Yogurt fortified with vitamin D—187 g	88
Beef liver—109 g	49
Cereal fortified with vitamin D—1¾ cup	40 (amount varies by product)
Egg yolk—1 full-size unit	41
Swiss cheese—31 g	6

Data from the National Institutes of Health Office of Dietary Supplements. Dietary Supplement Fact Sheet: Vitamin D. National Institutes of Health Office of Dietary Supplements; 2017. http://dietary-supplements.info.nih.gov/factsheets/vitamind.asp#h3. Accessed Jan 16, 2017.

While numerous indications regarding the role of vitamin D for the prevention and/or treatment of illnesses have appeared, the minimum value considered normal by researchers has led to an alarming epidemic of insufficiency of this vitamin (Looker et al. 2008; Ginde et al. 2009). It is assumed that public health campaigns promoting sun protection and lifestyle changes have played a role in this reduction. Therefore, important aspects regarding the sunlight environment, sun protection, and vitamin D status are discussed here.

Metabolism

More than 90% of vitamin D is obtained through cutaneous production promoted by sunlight (Reichrath 2006). When a photon of UV light B (UVB) radiation (290–315 nm) reaches the skin, it photoisomerizes the 7-dehydrocholesterol (7-DHC) in the cell membrane to pre-cholecalciferol (previtamin D_3), which is readily converted via heat isomerization into cholecalciferol (vitamin D_3). The peak circulating level of vitamin D_3 is reached during the following day and is then stored in body fat for release when needed. Vitamin D_2 (ergosterol), which is found in yeast and plants, is obtained via dietary intake and follows the same metabolic pathway of vitamin D_3. Vitamin D_3 enters the circulation through vitamin D-binding protein; it is hydroxylated in the liver to calcidiol (25(OH)D) and then is hydroxylated again, particularly in the kidneys, to its active form, calcitriol (1,25(OH)D) (Holick 1995).

However, both previtamin D_3 and vitamin D_3 are sensitive to UV-R, and continuous exposure to UVB causes photodegradation in the skin in inactive products (Webb et al. 1989).

The maximum cutaneous synthesis of vitamin D_3 is limited to 15–20% of the initial concentration of 7-DHC, with a production plateau occurring in less than 1 minimum erythema dose (MED) (Holick 1995; Webb 2006).

The 25(OH)D serum concentration is the value used to determine vitamin D status, which as well as 1,25(OH)D is under strict control by the endocrine system. The recommended minimum level of 25 (OH)D is currently controversial and under debate. The implications of vitamin D deficiency remain uncertain and many assumptions are still unproven.

The American Academy of Pediatrics and the American Society of Endocrinology consider a concentration of 20 ng/mL to be the cutoff point for vitamin D deficiency; however, the American Institute of Medicine suggests that 16 ng/mL is the appropriate minimum concentration, while the Endocrine Society recommends that 21–29 ng/mL be classified as vitamin D insufficiency (Chiu et al. 2013). These values have been associated with a lower risk of fractures and suppression of PTH elevation, a marker of deficiency, which stimulates the production of 1,25(OH)D for maintenance of intestinal calcium absorption (Hollis 2008). A level below 30 ng/mL (75 nmol/L) is considered "insufficient" by most specialists, and less than 20 ng/mL (50 nmol/L) is considered "deficient" (Malabanan et al. 1998; Bischoff-Ferrari et al. 2006).

Vitamin D intoxication, associated with hypercalcemia and hyperphosphatemia, is extremely rare and can be caused by doses greater than 50,000 IU/day and a 25(OH)D level above 150 ng/mL (Holick 2007).

The photodegradation of vitamin D_3 produced by the skin avoids vitamin D intoxication following sun exposure. With whole-body exposure to a single MED, the equivalent of approximately 10,000–20,000 IU of orally ingested vitamin D_3 is produced (Holick 2007; Vieth 1999).

Estimates vary, but about half of a MED from direct sunlight on the arms and legs can produce the equivalent of approximately 3000 IU of vitamin D_3. Sun exposure twice a week for 5–30 min at 12 noon has been suggested as sufficient for adequate vitamin D production in white populations. However, as discussed below, many factors influence the exposure time needed and it can therefore be variable (Holick 2007).

Coincidentally, cutaneous synthesis of vitamin D_3 as well as erythema (sunburn) occurs maximally at approximately the same wavelength of 296 nm UVB, although the erythema action spectrum extends to the UVA spectrum (Parrish et al. 1982 Fioletov et al. 2009). With solar radiation,

cutaneous synthesis of vitamin D_3 reaches maximum and plateaus after a short time, less than 1 MED (Gilchrest 2008).

Skin on the entire body is able to synthesize vitamin D, so when the whole body is exposed properly, production occurs more rapidly and with less risk of sunburn than when, for example, only the head is exposed. If only 10% of the skin is exposed to proper UVB radiation, the synthesis of vitamin D will take ten times longer than exposure of the whole body takes (Webb 2006). The required amount of time considered to be "suitable" exposure depends on many factors, including personal, behavioral, and environmental factors.

Environmental Factors that Affect the Cutaneous Production of Vitamin D

Solar Zenith Angle: Latitude, Season, and Time of Day

Before UVB solar radiation reaches the skin to start the synthesis of vitamin D, it must pass through the atmosphere. The main determinant of the potential UVB radiation available is the sun's angle in the sky compared to the vertical, or solar zenith, angle. The more directly above Earth that the sun is positioned, the lower the solar zenith angle and the lower the path traversed by the UV-R, meaning less chance of deflection or absorption of photons before they reach the skin (Webb 2006).

Three factors influence the solar zenith angle: latitude, season, and time of day. At higher latitudes, and especially in winter, the sun is not positioned as vertically in the sky at noon compared with at lower latitudes. Thus, the UVB radiation passes a long distance through the stratospheric ozone layer and atmosphere, attenuating until it reaches the Earth's surface (Table 2).

A series of studies published in the scientific literature have shown the relationship between sun exposure, skin cancer, and vitamin D synthesis. However, the shortage of medical data, particularly in developing countries, hinders the overall assessment of the impact of sun exposure on serum levels of vitamin D (Thieden et al. 2006; Godar et al. 2001; Webb et al. 1989).

Table 2 Factors influencing vitamin D production induced by ultraviolet radiation

Factors that increase the duration of sun exposure required for proper production of vitamin D_3
Increased zenith solar angle
Increasing latitude
Seasonal reduction in the length of days (winter)
Increasing the distance of time in relation to the half-day (morning, afternoon)
Lower altitude
Increased concentrations of ozone
Increased pollution
Thick cloud cover
Lower reflectivity of surrounding surfaces
Increased skin pigmentation
Decreased concentration of 7-dehydrocholesterol in the skin (age, burn victims)
Increased skin coverage with use of clothes
Sunscreen use

Schalka et al. 2014

According to a study published by De Paula Corrêa and Ceballos (2010), which evaluated the UVB radiation levels in the city of São Paulo, Brazil, over a period of 3 years, unintentional outdoor exposure, whatever the weather (taking into account overcast and rainy days), of only the hands and face for a period of 10 min daily would theoretically be sufficient for adequate vitamin D production in an individual with skin phototype II. Their study showed the UV index (UVI) measurements for the period 2005–2008. It was found that 65% of these UVI measurements, taken over 2 h at noon in São Paulo during summer, were very high (8–10), and extreme levels (UVI $>$ 11, according to the World Health Organization [WHO]) were evidenced at times.

Even during winter in São Paulo, 40% of the UVI measurements around noon proved to be high or very high. As a consequence, the authors suggest that UV levels are high enough to guarantee adequate production of vitamin D in human skin during incidental sun exposure during all months of the year, and the UV-R levels observed in São Paulo indicate that prevention of sun

overexposure is needed at any time of year (De Paula Corrêa and Ceballos 2010).

Altitude

Higher altitudes result in shorter distances to the sun and a less dense atmosphere, favoring the passage of UVB radiation. There is an approximately 4% increase in the amount of UVB radiation that reaches the exposed skin for each increase of 300 m in height (World Health Organization 2002).

Although neither a perfect measure of UVB radiation nor of the ability to synthesize vitamin D, the UVI is a non-dimensional representation of the intensity of the erythemal action of the weighted spectrum of irradiance (Fioletov et al. 2009).

Weather

UV-R is scattered and absorbed as it passes through an atmospheric distance. UVB radiation, which has a shorter wavelength, experiences greater attenuation than the UVA and visible spectrums of light, which have longer wavelengths (Webb 2006).

UVB radiation crosses a non-homogeneous atmosphere, and its features have significant influence on the amount of radiation that reaches the Earth's surface, a factor that probably became particularly important during the Industrial Revolution. Rickets occur due to impaired bone mineralization in calcium phosphate, which can be secondary to vitamin D deficiency or malnutrition. Although probably described since ancient times, the increase in cases following the advent of coal-burning factories and subsequent appearance of black clouds of smoke hovering over London at the end of the seventeenth century brought awareness of the bone-deforming diseases/rickets and led to speculation that pollution was to blame, although the mechanism was unknown and vitamin D had not yet been clearly discovered (O'Riordan 2006). Today, it is reasonable to assume that UVB rays being blocked due to absorption by particulate matter above the cities played a role in the manifestation of rickets. However, the tall buildings and narrow streets in the city, along with the prevalence of domestic work, also certainly decreased the population's exposure to the sun.

The concentration of ozone in the stratosphere is particularly important, since it absorbs a substantial proportion of UV-R with a wavelength less than 290 nm (previtamin D_3 synthesis is possible up to 270 nm) and attenuates UVB radiation above 290 nm (McLaughlin et al. 1982; Engelsen et al. 2005). The highest concentrations of ozone are usually found in higher latitudes toward the poles and it is found in lower concentrations in the tropics. Ozone levels in any location can change by up to 20% per day depending on the pattern of winds and pollution, which can produce ozone and other UVB-attenuating substances (Holick 2007).

Cloud coverage is also important in determining the UVB radiation available for the synthesis of vitamin D, and thick low clouds have a greater ability to reduce the amount of UVB that hits the ground. In fact, dense cloud cover can prevent 99% of UVB radiation from reaching the ground, thus preventing cutaneous synthesis of vitamin D, even at the Equator (Engelsen et al. 2005).

Environmental Factors in Brazil

A study recently conducted in Brazil made it clear that the sun protection recommendations, based on booklets and studies conducted mainly in the USA and Europe, are not adequate for the Brazilian environment. Most Brazilian territories are located in tropical and subtropical regions of the southern hemisphere, where the availability of solar radiation is quite high and ozone concentrations are naturally lower. For these reasons, UVI values observed throughout the country typically achieve higher levels according to the WHO, i.e., being of very high (UVI between 8 and 10) or extreme (UVI >11) damage to human health. In the north and northeast of the country, such values can be observed even prior to 9 a.m. at all times of the year. In the south and southeast, the UVI values at noon are characterized by marked seasonality, with extreme UVI values in summer and medium to high values in winter. However, it

is during the summer in the southeast region of the country that the Brazilian record UVI level of >15 can be observed.

This new knowledge about the distribution of UVI in Brazil constitutes an important factor for the mitigation of the skin cancer problem in the country. These very high UVI values require that solar protection (prevention) be part of every citizen's daily life. It is critical that effort be put into the harmonization and strengthening of preventive campaigns. Along with these efforts, it is important that opinion makers, including medical professionals, be aware during their daily contact with patients that the right judgment about sun exposure is an indispensable tool in preventing skin cancer.

Based on this basic knowledge, we conclude that there is no way to establish an appropriate or ideal time for exposure to the sun, as regional and meteorological variability is significant in different seasons and regions. For this reason, strengthening the recommendations regarding the need to avoid prolonged exposure and to use different forms of protection, during just about any time of year, is essential (Correa 2015).

Individual Factors Affecting Cutaneous Production of Vitamin D

Skin Pigmentation

Each individual's degree of skin pigmentation and age influences the production of vitamin D. The emergence of rickets and vitamin D deficiency among immigrants living in northern cities in the USA with dark skin or from India and UK, while similar populations in their birthplaces did not have this problem, led to speculation that the increased pigmentation in the skin of dark-skinned individuals could predispose them to vitamin D deficiency (Dunnigan et al. 1962).

While diet has often been a confounding factor, it has been proposed that research should be carried out to elucidate the role of the concentration of melanin in the vitamin D photoproduction. Melanin absorbs UV-R in the skin, which limits the number of photons available for converting 7-DHC molecules into previtamin D_3.

The Fitzpatrick skin phototype is commonly used to classify skin type and describes the melanin content of the epidermis and the skin reaction (sunburn or tanning) to UV-R after a prolonged period of non-exposure (Walker et al. 2003). These skin types also indicate the propensity for sun damage and the production of vitamin D. Skin phototypes I and II have fair skin that burns easily and rarely tans, while skin phototype III presents as fair skin but with a greater ability to tan and, consequently, is damaged less by UV-R. Skin phototypes I–VI have darker skin, with higher amounts of melanin; these skin types tan easily and rarely burn.

In theory, higher skin phototypes tend to decrease in the population as the distance from the equator is increased, with a higher prevalence of fair skin in higher latitudes, where UVB should be maximized for the production of vitamin D, and dark skins in equatorial regions, where UV-R is widely available throughout the year. Consequently, the risk of sunburn and skin cancer is increased when fair-skinned individuals are in the lower latitudes, and vitamin D deficiency, as mentioned earlier, is more prevalent in the polar regions (Hodgkin et al. 1973).

Age

Decreased vitamin D levels in the elderly are well-known, and there are multiple factors involved, including lack of sun exposure, food shortages, and poor absorption (Weisman et al. 1981; McLaughlin and Holick 1985).

The reduction in the efficiency of vitamin D synthesis with age has been analyzed in several studies that have shown that even with plenty of sunshine, serum levels of 25(OH)D are lower in healthy elderly than in young controls. Seasonal variations also decrease or even disappear with advancing age (Lester et al. 1977; Weisman et al. 1981).

The ability to synthesize vitamin D is based on the availability of 7-DHC. MacLaughlin and Holick demonstrated that with age there is a decrease in the amount of 7-DHC in the epidermis and, therefore, in the potential for producing vitamin D_3 (MacLaughlin and Holick 1985). The

authors obtained skin samples from six patients, all phototype III, with identical surface areas, and measured the amount of 7-DHC in the epidermis, which decreases by approximately half between the ages of 21 and 88 years. The specimens were then exposed to equal amounts of UV-R and the resulting synthesis of previtamin D_3 was quantified. Using the skin sample of an 8-year-old patient as a reference, in comparison one 18-year-old patient produced 80% of the amount of previtamin D_3, a 77-year-old patient produced 37%, and one 82-year-old patient produced 40%, inferring an approximately 2.5-fold decrease in previtamin D_3 synthesis capacity in the last years of life.

As thinning of the skin occurs with aging (Shuster et al. 1975; Dattani et al. 1984), it could be supposed that the reduction of previtamin D_3 synthesis capacity would be related to this; however, it has been found that previtamin D_3 synthesis is linearly related to the concentration of 7-DHC and not to skin thickness.

Although the production of vitamin D becomes less efficient with advancing age, Webb et al. proved that it was possible for elderly white nurses, all residents in Boston, Massachusetts, USA, to maintain adequate levels of 25(OH)D (defined as >15 ng/mL in their 1990 study) throughout the year by casual exposure to sunlight, without the need for oral supplementation (Webb et al. 1990). Oral supplementation of vitamin D dramatically reduced the number of patients with levels <15 ng/mL (to <5%) throughout the year; however, it more significantly minimized the seasonal decline in winter, when up to 40% of the supplemented group had previously shown serum concentrations of 25(OH)D <15 ng/mL. This value is well below the reference values used today. The article data did not allow the determination of the percentage of patients with values above 20 or 30 ng/mL.

Disorders that Decrease the Concentration of 7-Dehydrocholesterol

Intuitively, it could be assumed that malabsorption syndromes or drugs to reduce cholesterol could decrease the concentration of 7-DHC in the skin, but this theory does not seem to follow through. In contrast, a study involving vitamin D-deficient patients with Crohn's disease, primary biliary cirrhosis, and idiopathic pseudo-obstruction showed normal concentrations of 7-DHC in the skin (actually elevated compared with controls); therefore, the low concentration of 7-DHC was not the cause of vitamin D deficiency in this population of patients (Peterson et al. 1997).

No decreased levels of 25(OH)D have been found in studies involving statins and vitamin D (Dobs et al. 1991; Rejnmark et al. 2010). In fact, the use of statins has been associated with increased levels of 25(OH)D, although the mechanism for this is not yet clear (Castrillón-Perez et al. 2007; Aloia et al. 2007).

Behavioral Factors that Affect Cutaneous Production of Vitamin D

Avoiding Sun Exposure

Prevention of exposure to UVB radiation can be carried out in several ways, such as by avoiding it altogether (staying indoors), covering the skin with clothing, or applying sunscreen.

A large study by Glass et al. involving more than 1400 white women conducted in the UK examined the relationship between vitamin D, skin pigmentation, and exposure to UV rays (Glass et al. 2009). It was observed that higher phototypes (III and IV) had higher serum levels of 25(OH)D (mean 32.9 ng/mL) than lower skin phototypes (types I and II) (average 28.5 ng/mL, $p < 0.0001$). These data showed an inclination towards higher sun exposure by patients of darker skin, which was positively correlated with their vitamin D status.

Malvy et al. conducted a similar study in France, involving 1191 individuals, and also observed that serum levels of 25(OH)D were lower in light-skinned individuals ($p < 0.024$) (Malvy et al. 2000). Studies of individuals who work under the sun, such as farmers and lifeguards, revealed high levels of 25(OH)D, with average concentrations between 54 and 65 ng/mL (Vieth 1999).

Although most sun exposure is associated with higher levels of vitamin D, the interesting results of Binkley et al. suggest that abundant exposure may not be enough to improve the vitamin D status in all individuals (Binkley et al. 2007). The substantial variability in the study suggests that there are likely to be other factors that influence the cutaneous production of vitamin D or its subsequent metabolism, which have not yet been fully elucidated.

Different genetic requirements for performing the physiological functions of vitamin D may exist as well as the need for a lower optimal level in some populations. For example, African Americans have lower levels of 25(OH)D than white individuals, but have higher bone density and a lower number of fractures relating to osteoporosis (Aloia 2008).

A recent study suggested that the balance between the UVB dose that can trigger erythema and the correct dose for vitamin D production can be achieved through an occasional specific behavior in relation to sun exposure; therefore, photoprotection can be optimized and create a tendency towards benefit. According to the data, people living in low latitudes could be exposed to the sun for a certain period of time at noon and avoid the sun at other times. This would lead to production of an adequate amount of vitamin D via the MED necessary for a phototype II individual. For this, forearms and bare hands should be exposed to the sun daily at noon (in cloudless weather) for 11 min in winter or 5 min in summer. Exposure at times outside of midday may represent an increase of an up to 24% greater erythema dose and an up to 12 times longer time of exposure may be required than the minimum amounts needed at noon (Silva 2014).

Clothing

Clothing is an additional barrier that UVB radiation must break through to reach the 7-DHC. In a similar way to sun protection factor (SPF) sunscreen, different types of tissue can be assigned an equivalent UV protection factor (UPF) (Morison 2003).

The UPF measures the degree of transmission of UV-R through the tissue, e.g., a UPF of 50 means that only 2% (1/50) of UV-R is transmitted through the tissue. A thick brim/jean fabric tissue may have a UPF of 50+, while a lightweight cotton shirt may have a UPF <10 (Sayre and Huges 1993).

Darker colors absorb the UV-R better; therefore, the same fabric can provide greater UPF. The composition of the fabric determines how absorbent it is. For example, polyester protects more than cotton and natural cotton is more effective than bleached cotton (natural cotton has pigments that absorb UVB) (Gambichler et al. 2002).

Additives such as titanium dioxide and fluorescent whitening agents can be used by manufacturers to increase the UPF. The fabric getting wet through sweating or contact with water can, however, cause different responses and may reduce the UPF by half, e.g., in a white cotton shirt. Most research focuses on the analysis of clothing and UPF but does not address the consequences on vitamin D. According to the authors, certain fabrics can prevent the formation of vitamin D in the covered areas of the skin (Matsuoka et al. 1992; Salih 2004).

Sunscreen

The proper application of sunscreen can prevent the damage to the skin caused by UV-R, but the same blocked UVB is also required for the production of vitamin D (Sedrani et al. 1983; Thompson et al. 1993; MacNeal and Dinulos 2007). However, although intuitively we suspect that the proper use of sunscreen may prevent adequate synthesis of vitamin D, there are few studies examining this issue (Naylor et al. 1995; Darlington et al. 2003).

Evidence that the application of sunscreen would hinder synthesis of vitamin D, taken from research that analyzed individual doses in controlled environments, could be true, but the results of larger-scale studies are not consistent with these findings.

Maia et al. assessed serum concentrations of 25(OH)D and PTH in groups of individuals with and without guidance for photoprotection, all

residents in São Paulo. The authors found a significant difference between the levels of 25(OH)D, which were higher in the photoexposed group (35.4 ng/mL [range 21.86–72.20 ng/mL]) than in the photo-protected group (29.2 ng/mL [range 23.10–45.80 ng/mL]). Despite these differences, there were no vitamin D-deficient individuals in the sample. It was concluded that the everyday solar UV-R was enough to promote adequate synthesis of 25(OH)D (Maia et al. 2007).

A preliminary cross-sectional study conducted by Kligman et al. reported that the use of sunscreen by seniors in Arizona, USA, was positively associated with serum 25(OH)D (Kligman et al. 1989). A similar study, based on data collated from questionnaires, was performed by Kimlin et al., which involved a wide range of Australian subjects aged 18–87 years. The authors found no statistically significant association between the status of 25(OH)D and the use of sunscreen, and participants who used sunscreen showed some of the highest levels of 25(OH)D. In this case, it was assumed that the use of sunscreen was probably an indication of increased sun exposure (Kimlin et al. 2007).

One explanation for the lack of a negative correlation (and sometimes positive correlation) between vitamin D status and the use of sunscreen was provided by Thieden et al. The authors concluded that the sunscreen was applied frequently on the days when high amounts of sun exposure were expected in order to avoid burns. Thus, the use of sunscreen was associated with a more frequent and longer duration of exposure to sunlight (Thieden et al. 2005).

Therefore, an active sun-seeking behavior would be able to counteract any vitamin D synthesis attenuation that sunscreen, theoretically, could cause. A survey by Stender et al. found that sunscreen users often had burns, again showing improper or inappropriate use, as well as increased sun exposure in comparison with individuals who use sunscreen less frequently (Stender et al. 1996).

A recently published study showed that the prevalence of vitamin D deficiency among patients with systemic lupus erythematosus is high. This fact was attributed to photoprotection measures in association with the intrinsic factors inherent to the disease. Low levels of vitamin D in these patients could contribute not only to a decrease in bone mineral density and an increased risk of fractures but could also have undesirable effects on the immune response, reinforcing mechanisms of loss of tolerance and autoimmunity. It was suggested that the vitamin D status of patients with systemic lupus erythematosus should be monitored periodically and they should be treated with the goal of achieving vitamin D levels between 30 and 40 ng/mL (Sanguesa-Gomez et al. 2015).

Avoiding exposure to sunlight is a mandatory in photodermatoses; however, the need for oral supplementation with vitamin D in these patients is still uncertain. A study published in 2016 investigated the seasonal variation in vitamin D levels and bone formation markers in healthy subjects compared to patients with systemic lupus erythematosus who had restricted photoprotection (Bogaczewicz et al. 2016).

Thirty-four healthy inhabitants of the Lodz region in Poland, a country in Central Europe (51° and 52° latitudes north), were analyzed at baseline within 2 weeks of peak sun exposure during recreational activity whilst on vacation and then after 8 and 16 weeks. The group of patients using photoprotection measures consisted of 104 patients diagnosed with systemic lupus erythematosus. The serum levels of 25(OH)D, procollagen type I, N-terminal propeptide (PINP), and osteocalcin were measured. The results showed that serum concentrations of 25(OH)D were lower and that vitamin D deficiency was more common in patients who were using additional photoprotection measures than in healthy subjects during periods of cold and heat ($p < 0.05$). In healthy individuals, vitamin D deficiency was more prevalent after 8 and 16 weeks than at baseline ($p < 0.001$). The average level of PINP was 39.56 (30.51–53.22) ng/mL, and was elevated in 50% of subjects, while osteocalcin was 18.88 (13.52–21.33) ng/mL, within the reference range.

It is possible to conclude that the diagnosis of vitamin D deficiency and oral supplementation in patients using photoprotection measures should be included in clinical practice. Maximum levels of 25(OH)D are likely to be achieved via cutaneous synthesis of vitamin D during the summer and

decrease over time, starting to fall from August or, possibly, the end of summer in the northern hemisphere (Bogaczewicz et al. 2016).

A study published in 2015 showed a high prevalence of vitamin D deficiency in patients with xeroderma pigmentosum (XP), i.e., patients with limited photoprotection (Kuwabara et al. 2015). Twenty-one patients with XP (aged 6–25 years) were evaluated regarding their intake of vitamin D and serum levels of 25(OH)D and PTH. Vitamin D intake was measured using a food-weighing method for 2 days.

The results from this study showed that the average intake of vitamin D was 4.1 μg/day and the average concentrations of 25(OH)D and PTH in serum were 7.7 and 49.9 pg/mL, respectively. Serum 25(OH)D levels were below 10 ng/mL in 76% of patients, indicating considerable vitamin D deficiency. Vitamin D intake and 25(OH)D serum levels were significantly lower in patients receiving enteral nutrition than with oral ingestion. Multivariate analysis revealed that enteral nutrition was a significant predictor of decreased serum levels of 25(OH)D (β-coefficient $= -0.59$, $p = 0.03$). Therefore, it was concluded that vitamin D deficiency is highly prevalent in patients with XP and supplementation should be considered to prevent adverse skeletal consequences. Moreover, determination of the recommended dietary intake (RDI) of vitamin D is a difficult issue in these patients due to a deficiency in its cutaneous production. Further studies in patients with XP should be conducted to determine the optimum RDI of vitamin D for these patients (Kuwabara et al. 2015).

Final Considerations

Benefits of Vitamin D

The only known benefit of vitamin D is its relationship to bone health as it is involved in calcium metabolism. Adequate vitamin D levels are related to the prevention of rickets and osteoporosis. However, the evidence that vitamin D reduces the risk of developing non-skeletal chronic diseases is inconsistent and inconclusive and does not meet the criteria of cause and effect (Ross et al. 2011) (Table 3).

Table 3 Vitamin D and disease

Disease	Evidence[a]
Bone health	+++
Cancer	+
Multiple sclerosis	+
Macular degeneration	+
Atopic dermatitis	+
Melanoma	+
Hypertension	+/−
Colorectal cancer	+/−
Cardiovascular disease	−
Type 2 diabetes mellitus	−
Rare cancers[b]	−
Depression	−

[a]The evidence is classified by the authors from the strongest evidence (++++) to no association (−)
[b]Rare cancers are endometrial, esophageal, stomach, renal, ovarian, pancreatic, and non-Hodgkin's lymphoma

Vitamin D Serum Levels

The definition of vitamin D deficiency based on 25 (OH)D serum is controversial in the literature. Values above 30 ng/mL (>75 nmol/L) are considered satisfactory by all authors. By consensus, levels below 20 ng/mL (<50 nmol/L) can be considered as vitamin D deficiency, because this value corresponds to the needs of more than 97.5% of the population. However, there is controversy relating to values ranging between 20 and 30 ng/mL, which some authors define as an intermediate situation, referred to as "unsatisfactory." The change in the cutoff point can produce a significant increase in the number of individuals classified with deficiency, as shown in some more alarming statistics.

World epidemiological data show that only about 30% of individuals have a vitamin D index of less than 20 ng/mL and can therefore be classified as deficient (Binkley et al. 2010).

Sun Exposure and Vitamin D

UVB, with peak activity at 296 nm, has a function in vitamin D metabolism, converting 7-DHC in the

epidermis to previtamin D_3. From there, a sequence of metabolic hydroxylation reactions occurs in the liver and kidneys, producing of the active form of vitamin D (1,25-dihydroxycholecalciferol).

The estimated dosage of UVB required to produce 1000 IU of vitamin D is 0.25 MED when approximately 25% of the total body area is exposed. This is considered to be a small dose compared with that required to produce erythema.

In a country with high levels of sunstroke, such as Brazil, a few minutes of exposure of only the hands and face to the external environment, whatever the weather, would be sufficient for vitamin D production. Therefore, there should be greater concern regarding the risks associated with sun exposure than those related to its non-exposure.

Regarding sun exposure time, we know that the UVB radiation level in the period prior to 10 a.m. and after 3 p.m. (disregarding daylight saving time) is minimal and does not justify sun exposure during these periods, particularly with the intention of producing vitamin D.

Sun Exposure and Skin Cancer Development

The incidence of non-melanoma skin cancer and melanoma has been growing around the world for decades, and they are the most common cancers in the body. Furthermore, the causal relationship between sun exposure and the development of squamous cell carcinoma is well-established in the literature and several studies also point to the involvement of solar radiation in the development of basal cell carcinoma and melanoma.

Sun Protection and Vitamin D

We know that the proper use of sunscreen reduces the amount of UVB radiation that reaches the skin surface in a significant way and can, thus, theoretically interfere with the production of vitamin D. However, in practice we know that regular use of sunscreen does not lead to vitamin D deficiency.

A possible explanation would be that users do not apply the proper amount of sunscreen with the frequency and regularity recommended, and, therefore, a sufficient amount of UVB radiation would reach the skin's surface for vitamin D production. Thus, the use of sunscreens, as commonly applied by users, cannot be considered a predisposing factor for the development of vitamin D deficiency.

Conclusion

Many external factors affect the amount of UVB available and its capacity to influence vitamin D photosynthesis beyond the influence of each individual's genetic potential response. Therefore, it is difficult to make general statements correlating the duration of sun exposure with the status of vitamin D.

Recommendations for the "ideal" exposure seem overly simplified given the complexity and individuality of the final determination of vitamin D synthesis. With the continuous expansion of findings regarding the functions of vitamin D, the definition of "adequate" remains uncertain, and indirect markers previously considered for the evaluation of deficiency, such as high PTH, probably do not address this panorama of factors effectively.

The risk of sun damage and skin cancer with excessive exposure to UV rays and the availability of oral vitamin D supplementation further hamper the establishment of guidelines defining the safe and optimal levels of sun exposure needed to maintain adequate concentrations of vitamin D. Theoretically, sunscreens applied at the recommended concentration (2 mg/cm^2) reduce the synthesis of vitamin D. Nevertheless, in practice, and in line with some studies, the use of sunscreen does not lead to significant reduction in serum levels of the vitamin. However, other methods of sun protection, such as constantly avoiding the sun, seeking shadows, or wearing clothing with photoprotective capacity, can result in vitamin D insufficiency in the serum.

Thus, vitamin D supplementation should be considered for risk groups (Kannan and Lim. 2014).

Patients who are advised to avoid the sun and have restricted photoprotection due to their underlying disease, as in the case of photodermatoses (skin disorders that present with an increased risk of skin cancer), such as XP, epidermodysplasia verruciformis, and prior melanoma, or who attend with photosensitivity, such as in lupus erythematosus, should be periodically monitored in relation to vitamin D status, analyzed individually, and supplemented according to their needs.

Take-Home Messages

Based on the above assumptions, we have the recommendations regarding vitamin D:

- Intentional sun exposure should not be considered as a source of vitamin D production or for the prevention of disability.
- Photoprotective measures, such as wearing clothing, hats, and sunglasses, and a lack of exposure to the sun in extreme times (from 10 a.m. until 3 p.m.) continue to be the most appropriate recommendation for the prevention of skin cancer and photoaging.
- Based on the position of the American Institute of Medicine, patients with 25(OH)D serum levels <20 ng/mL are considered to have insufficient vitamin D.
- Patients considered to be at risk of developing vitamin D deficiency should be monitored by periodic examination and can use dietary sources and vitamin supplementation to prevent vitamin D deficiency.

Factors increasing the risk of developing vitamin D deficiency:

- Infants receiving exclusive breastfeeding
- Elderly (aged skin produces less vitamin D)
- Individuals with low sun exposure
- Climate conditions
- Rigorous use of sun protection measures
- Skin cover in religious practices
- People with high phototypes (skin types V and VI)
- Patients with malabsorption syndrome
- Morbid obesity.

The recommended daily dose of vitamin D for deficiency prevention in at-risk individuals is as follows:

- 0–12 months: 400–1000 IU/day
- 1–18 years: 600–1000 IU/day
- 19–70 years: 1500–2000 IU/day
- >70 years: 1500–2000 IU/day

Finally, the Brazilian Society of Dermatology (SBD) believes that the Policies for prevention of skin cancer through conscious photoprotection is a priority measure in terms of public health for Brazil in the field of dermatology (Schalka et al. 2014).

Cross-References

- ▶ Chemical and Physical Sunscreens
- ▶ Oral Photoprotection
- ▶ Photoprotection: Concept, Classification, and Mechanism of Action

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Part IV

Topical and Oral Treatments in Cosmetic Dermatology

Cleansers

Carmelia Matos Santiago Reis and Eugênio Reis-Filho

Abstract

Cleansing the skin is the most important skin care act. Cleansers contain at least one surfactant. Surfactants enable the solubilization of oils, dirt, sebum, and other unwanted substances from the skin, allowing these materials to be washed away. There are four categories of cleansing agents: soaps, synthetic detergents, lipid-free lotions, and prescription antimicrobials. There are four categories of surfactants based on their molecular charge or lack of molecular charge: anionic, cationic, amphoteric (dual charge), and nonionic. The skin needs in each age group are diversified. Adequate skin care is regarded as a major strategy for maintaining the skin barrier, skin integrity, and skin health.

Keywords

Soap • Syndet • Surfactant • Detergents • Skin care • Cleansers

Contents

Introduction

Cleansing the skin is the most important skin care act, removing dirt, sweat, sebum, and oils from the skin. Selecting the proper cleanser is key to maintaining the skin acid mantle and preserving skin health. The skin acid mantle works as a barrier function as well as bacterial flora regulation. A good cleanser should provide optimal skin cleansing while minimizing barrier damage (Draelos 2004, 2011; Draelos et al. 2013).

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Many of the environmental impurities and cosmetic products are not water soluble, and so washing the skin with simple water would not be sufficient to remove them (Mukhopadhyay 2011).

Cleansers contain at least one surfactant, or surface-acting agent, a class of molecules that have hydrophilic and hydrophobic domains. Surfactants are responsible for its cleansing action. Surfactants aid in the uplifting of dirt and solubilization of oily soils, emulsifying these fat impurities soluble in water (Draelos et al. 2013; Ananthapadmanabhan et al. 2004; Mukhopadhyay 2011).

The interaction of cleanser surfactants with the stratum corneum proteins and lipids can be deleterious to the skin. Cleanser surfactants can cause immediate dryness, barrier damage, erythema, irritation, and itching (Ananthapadmanabhan et al. 2004).

Surfactants

Surfactants are usually organic compounds that are amphipathic, that is, they contain both nonpolar or hydrophobic groups (their "tails"), typically a long alkyl chain, and polar or hydrophilic groups (their "heads"). Therefore, they are soluble in both organic solvents and water (Corazza et al. 2010).

Surfactants' unique chemistry enables the solubilization of hydrophobic compounds present in oils, dirt, sebum, and other unwanted substances from the skin, allowing these materials to be washed away with greater ease than what could be achieved with water alone (Draelos et al. 2013). Surfactants can also assemble, into the solution, the aggregates known as micelles. In these aggregates, the lipophilic ends of the surfactant molecules dissolve in the oil, while the hydrophilic-charged ends remain outside, shielding the rest of the hydrophobic micelle. Surfactants reduce surface tension of water by adsorbing at the liquid–gas interface and also lower the interfacial tension between oil and water by adsorbing at the liquid–liquid interface (Corazza et al. 2010).

The cleanser's pH may contribute to damage the stratum corneum. The normal pH of the skin surface is in the acidic range, with estimates ranging from 4.0 to 6.5. Traditional soaps are alkaline in nature and are thought to impair the lipid bilayer of the stratum corneum barrier, leading to the potential for irritation by removing intercellular lipids. Synthetic detergent cleansers (syndets) are formulated to have a neutral (7.0) or slightly acidic pH to ensure skin compatibility (Takagi et al. 2015).

It is well known that soap-based cleansers have a higher potential to irritate the skin than cleansers with synthetic surfactants (syndets). Recognition of mildness as an important property of cleansers has spawned the development of therapeutic cleansers that are compatible with patient skin types and topical therapies. There are four categories of cleansing agents: soaps; synthetic detergents; lipid-free lotions, which contain fatty alcohols that serve as emollients or humectants; and prescription antimicrobials. Among the factors affecting skin compatibility are pH and type of surfactant (Draelos 2004).

Natural Surfactants: Soaps

Soap is a common term used by many as synonymous with cleanser. However, soap is a specific cleanser with a definite chemical composition. Soap is defined as a chemical reaction between a fat and an alkali, resulting in a fatty acid salt with detergent properties. Most cleanser bars produced around the world use soap as the cleansing agent.

Soaps are effective cleansers; they can dissolve fat-soluble and water-soluble components of the skin surface. Because of the alkaline properties, soaps can increase skin surface pH and have greater potential to irritate the skin and affect the skin's barrier repair mechanism. The pH of normal soaps is within the range of 9.5–11.0 (Ananthapadmanabhan et al. 2004).

The high pH of these cleansers is excellent for thoroughly removing sebum, but it can also damage the intercellular lipids in diseased or sensitive skin. If this high pH is maintained for more than 4 h, due to insufficient rinsing or frequent use of wrong products, it could worsen the skin condition (Abbas et al. 2004).

Soap-based bars are harsh to the skin. Common dermatological problems associated with

soap use include erythema, dryness, and itchiness, particularly in cold weather.

Unlike mild syndet surfactant-based cleansers, harsh cleansers such as soaps induce perceivable skin tightness, a sensation that manifests about 5–10 min after washing with a cleanser (Ananthapadmanabhan et al. 2004).

The only major brand of true soap still available on the market today is Ivory soap (Procter & Gamble, Cincinnati, Ohio).

Modern refinements have attempted to adjust its alkaline pH, possibly resulting in less skin irritation, and incorporate substances to prevent precipitation of calcium fatty acid salts in hard water, known as "soap scum." Nevertheless, modern soap is basically a blend of tallow and nut oil, or the fatty acids derived from these products, at a ratio of 4:1. Increasing this ratio results in "superfatted" soaps designed to leave an oily film behind on the skin. The use of mitigating components reduces the irritancy of soap bars and has led to the development of superfatted soaps, transparent soaps, and combination bars (combars).

Modern bar soaps can be divided into three different types – soap subsets:

1. *Superfatted soaps*. Incomplete saponification leaves unreacted fatty acids or oils in the product, resulting in superfatted soaps. Superfatting can also be achieved by adding a desired quantity of fatty alcohols, fatty esters, or fatty acids during processing. Superfatting improves product moisturization and mildness, as well as the lather, and mush and wear properties, providing a protective film on the skin. They contain greater amount of lipids, such as triglycerides, lanolin, paraffin, stearic acid, or mineral oils (Abbas et al. 2004; Mukhopadhyay 2011).
2. *Transparent soaps/glycerin bars*. Early attempts to minimize the damage potential of soaps involved the incorporation of glycerol in soap bars and the production of transparent glycerin bars. Transparent soaps still have high-level amounts of natural soap and an alkaline pH, which tend to increase the irritancy, but are generally considered to be mild, owing to the presence of the glycerin, a humectant, and low total fatty content. Considerable advances have taken place during the past few decades in transparent soap formulation development, technology, and manufacturing (Ananthapadmanabhan et al. 2004; Abbas et al. 2004).
3. *Combination bars (combars).* The major component of combars is natural soap. Most of them contain superfatted soap as well as a synthetic surfactant, which together reduce the irritancy of the product, although the pH remains high, at about 9.0–9.5. While combars are, in general, less irritating than soaps, they are less mild than syndet bars (Abbas et al. 2004).

Syndets

Following the development of true soaps came the invention of synthetic detergents. Synthetic detergents are known as syndets and contain less than 10% real "soap." They are known as cleansers with non-soap-based surfactants. Rather than possessing a highly alkaline pH, these products can be made with a pH adjusted to 5.5–7. This more neutral pH is similar to the normal acid mantle pH of the skin, causing less irritation (Draelos 2011).

The skin cleansing technology has evolved from basic soap to syndet bars and shower gels with moisturizing lipids, emollients, occlusive, and humectant agents, which offer other skin care benefits beyond cleansing.

The synthetic detergents can be anionic, amphoteric, and nonionic. Addition of cationic polymers to skin cleansers can further protect the skin and improve moisturization. To further improve cleanser mildness, adding hydrophobically modified polymers (HMPs) as silicone to cleansers that contain surfactants can help to create polymer–surfactant complexes that are even less irritating to the stratum corneum lipid barrier. HMPs interact with the hydrophobic tails of other surfactants, leading to the formation of larger surfactant structures and a reduction in the surfactant dynamics. HMPs also lower the effective concentration of free surfactant micelles in solution and facilitate

foam formation. The potential damage to the skin has been minimized with the use of mild surfactants, as well as the incorporation of beneficial agents (Draelos 2011).

The first breakthrough in mild cleansing occurred in the 1950s with the introduction of syndet bars, with mild alkyl isethionate as the synthetic surfactant. Incorporation of a long-chain fatty acid lipid cocktail, often referred to as a "moisturizing cream," has enhanced the mildness and moisturizing properties of syndet bars. Dove® was the first syndet bar sold in the market in 1955. Since then, other syndet bars have emerged (Ananthapadmanabhan et al. 2004; Abbas et al. 2004).

Others: Body Wash and Shower Gel

Liquid cleansers introduce new opportunities for milder formulations than those used in bars. Liquid cleanser technology can be designed to deposit and deliver beneficial agents onto the skin from a wash-off system. Beneficial agents such as petrolatum, triglycerides, and sterols can be deposited on the skin during cleansing and reduce the visible signs of dryness, providing a barrier that helps reduce the skin's water loss. Emollients minimize barrier damage in two fundamental ways: first, by reducing the interactions between the cleanser surfactants and the skin proteins and lipids and, secondly, by restoring those that are inevitably lost during a wash period.

The liquid system process selects milder surfactants and surfactant mixtures from a much wider array of surfactants. The syndet-based liquid cleansers use a combination of anionic and amphoteric surfactant mixtures to enhance mildness. To minimize these effects, some modifications have been made in these products.

Liquid detergents allow the creation of liquid surfactant solutions at a pH below 7 and result in less damage and drying of the skin.

Developing cleansers that effectively deliver moisturizing benefits is a technical challenge: it requires depositing skin care agents, which are normally removed by skin cleansers, under wash-off conditions (Ananthapadmanabhan et al. 2004).

Classes of Surfactants

There are four categories of surfactants based on their molecular charge or lack of molecular charge: anionic, cationic, amphoteric (dual charge), and nonionic (Draelos 2004).

The type and amount of surfactant in a cleansing agent have a bearing on its drying and irritancy potential (Mukhopadhyay 2011).

Anionic Surfactants

Anionic agents have a negative charge in their hydrophilic head. The members of this group are typically used as primary surfactants in cleansers because of their easy solubility in water, excellent lather characteristics, higher cleansing power, and good wetting properties but moderate disinfectant properties (Corazza et al. 2010; Biasi 2012).

They are also used as primary surfactants in cleansers, because of their moderate final product cost, although they are powerful skin irritants. Common approaches to lowering the tendency of anionic surfactants to damage proteins include increasing the size of the head/polar group of the surfactant and using a combination of anionic surfactants with amphoteric or nonionic surfactants. In general, for a surfactant with a given chain length, the larger the head-group size, the lower its tendency to cause protein swelling (Corazza et al. 2010; Ananthapadmanabhan et al. 2004).

Typical anionic agents used in detergents include soaps (salts of fatty acids) containing carboxylate ions and synthetic surfactants, such as alkyl ether sulfates, alkyl ethoxy sulfates, alkyl acyl isethionates, acylglutamates, alkyl taurates, alkyl phosphates, alkyl sulfonates, and alkyl sulfosuccinates (Corazza et al. 2010).

A well-known alkyl sulfate, widely used in personal care products, is sodium lauryl sulfate (SLS), an anionic surfactant, wetting agent, and detergent. This anionic agent is associated with the greatest potential for skin penetration and skin irritation, causing large alterations in barrier properties (Corazza et al. 2010).

The corresponding ethoxylate (sodium laureth sulfate (SLES)) is the favorite primary surfactant in body wash/shower gel and shampoo, because of its good cleansing power and its low cost, even if it has some irritant potential. Actually, new mild cleansers are marketed, and they are based on other surfactants, such as sodium cocoyl isethionate (Corazza et al. 2010).

According to recent studies, alkyl sulfates and alkyl sulfosuccinates have the highest cleansing power, followed by very expensive acyl glutamate and triethanolamine soaps (Corazza et al. 2010).

Cationic Surfactants

Positively charged cationic agents have lower detergent properties than anionic surfactants. They do not produce abundant lather; they are irritating as well as anionic and are more cytotoxic. On the other hand, because of their considerable bactericidal activity against a wide range of microorganisms, they may be used as antimicrobial preservatives, rather than as surfactants. Cationic surfactants are common conditioner ingredients (hair-conditioning agents) and antistatic agents in shampoo (Corazza et al. 2010; Biasi 2012).

The most common cationic surfactants are amine salts and quaternary ammonium salts (cetrimide and benzalkonium chloride). Cetrimide solutions (0.1–1%) may be used for cleaning wounds and burns on the skin, for disinfection of medical instruments, and as hair-conditioning agent in shampoo. Benzalkonium chloride (0.5–2%) is also used as a preservative for ophthalmic products (Corazza et al. 2010; Biasi 2012).

Amphoteric Surfactants

Amphoteric surfactants exhibit the properties of anionics or those of cationics, according to the pH of the solution. At a high pH, they behave as anionic agents and, at low pH, as cationic (Corazza et al. 2010; Biasi 2012).

The members of this group have good cleansing power, good lather characteristics, and a moderate antimicrobial activity. Skin and mucosal tolerability is excellent, and they are compatible with different pHs. Therefore, they are widely used in combinations to enhance mildness (Corazza et al. 2010; Biasi 2012).

The final cost of amphoteric agents is not negligible, but they are extensively used in liquid cleansers, moisturizing body wash, shower gel, shaving products, shampoo, toothpastes, and contact lens detergents. Commonly used amphoteric surfactants include cocamidopropyl betaine, cocoamphoacetate, and cocoamphodiacetate (Corazza et al. 2010; Biasi 2012).

In particular, one of the most common agents in this group is cocamidopropyl betaine. It has been increasingly used in shampoos and liquid cleansers since its introduction in the 1970s, because of its moderate irritancy potential. This surfactant is also considered as a viscosity builder and foam booster. Cocamidopropyl betaine is responsible for increasing cases of allergic contact dermatitis (ACD) caused by shampoos and detergents. Nevertheless, according to the latest studies, the real sensitizers in these cases seem to be impurities, such as the parent compound dimethylaminopropylamine, which may be present in some sources of the surfactant (Corazza et al. 2010).

Regarding amphoacetates, they are used in cosmetics as gentle surfactants with low irritancy potential (at concentrations of 0.1–50%) (Corazza et al. 2010).

Nonionic Surfactants

Nonionic agents have no electric charge in the head, being thus compatible with all other surfactants. Their cleansing power and lather characteristics are quite weak. Furthermore, the members of this group have a relatively low potential toxicity, and they are considered the most gentle surfactants but also the most expensive ones (Corazza et al. 2010; Biasi 2012).

They are the second most often used group, after the anionic detergents, in particularly as secondary detergents in combination with anionics. They are also used as thickeners for shampoos and

as emulsifiers and suspending agents in cosmetics, pharmaceutical products, and foods (Corazza et al. 2010; Biasi 2012).

Commonly, nonionic agents are considered the lowest irritants to the skin among the different types of surfactants. Nevertheless, some authors noticed that nonionic surfactants alter the cutaneous lipid layer more often than anionics, because they can solubilize fatty acids and cholesterol in the skin. Nonionic surfactants have a greater tendency to dissolve stearic acid than do anionic surfactants, which may translate into greater skin de-fatting if cleansers with excessive levels of nonionic surfactants are used (Ananthapadmanabhan et al. 2004).

Among the compounds belonging to this group are alkyl polyglucosides, such as coco-glucoside, lauryl glucoside, and decyl glucoside. Another common nonionic agent is cocamide DEA (coconut diethanolamide), widely used in personal care products for its thickener property and foam booster, as well as in metalworking fluids as a corrosion inhibitor. In addition, this class of surfactants includes fatty acid esters of fatty alcohols, sorbitan esters, sucrose, and cholesterol derivatives used as emulsifiers (Corazza et al. 2010).

Cleansers in Different Ages

The skin needs in each age group are diversified. Adequate skin care is regarded as a major strategy for maintaining the skin barrier, skin integrity, and skin health. So it is important to know the differences in order to indicate the most appropriate cleanser for every situation (Biasi 2012; Blume-Peytavi et al. 2009).

In the newborn, the skin barrier is not fully formed until the first year of life, thus requiring a careful choice of a cleanser. The skin of infants is morphologically and functionally different from the skin of adults. Within their first days of life, babies undergo various adaptation processes needed to accommodate the transition from the wet uterine environment to the dry atmosphere (Biasi 2012; Blume-Peytavi et al. 2012).

Infant skin has higher stratum corneum hydration values than adult skin, higher transepidermal water loss (TEWL) values, higher water permeability expressed as water absorption and desorption rates, and less natural moisturization factor. Neonatal and infant skin differs from adult skin in thinner layers and less amount of sebum; the amount of natural moisturizing factor and water content in the child's skin horny layer are smaller and are more prone to oxidative stress. Special care procedures are required to ensure healthy development and to protect the skin from irritation and inflammation, as well as to create a sense of well-being. Non-alkaline liquid cleansers are recommended to prevent dryness and irritation, preferably products containing emollients as well as soft products for the skin and eyes. A simple tip is to use products suitable for child's skin (Biasi 2012; Blume-Peytavi et al. 2012).

At puberty, the levels of circulating androgens increase dramatically, causing various changes in the skin, including increasing the size of the sebaceous glands and the production of sebum. There is a high prevalence of acne in that period, and the proper choice of this condition and even therapy is reducing the amount of injuries. Choosing the right cleanser for acne-prone skin will be discussed later in this chapter (Biasi 2012).

The aging process is associated with inevitable anatomical, morphological, physical, and psychosocial changes. These changes also compromise the skin. The skin of elderly is a result of both intrinsic aging due to the passage of time and extrinsic aging as a consequence of environmental damage, primarily due to ultraviolet (UV) irradiation. In the elderly skin, cell replacement is continuously declining; the barrier function and mechanical protection are compromised. The epidermis is thinner, wound healing and immune responses are delayed, and there is a reduced number of Langerhans cells. The reduced skin elasticity and sebaceous and eccrine and apocrine sweat glands compromised the thermoregulation and decreased sweat and sebum production. All these changes reduce the skin's ability to retain water and predispose to dry skin. It is recommended to avoid alkaline products and the use of agents with emollient action (Kottner et al. 2013; Tran et al. 2014; Biasi 2012).

On the cellular level, the content of natural moisturizing factors and lipids in the stratum corneum is reduced leading to decreased lamellar bilayers and poorer water-holding capacity. Chronic diseases, drugs, and environmental factors including detrimental skin care habits damage the skin barrier integrity in the elderly (Kottner et al. 2013).

One of the most common dermatological diagnoses in the elderly is xerosis cutis with prevalences ranging from 30% to 85%. Special bathing products and cleansing procedures, moisturizers, barrier creams, or other leave-on products are widely recommended for preventing and treating xerosis. For preventing skin injuries, the use of special soaps and synthetic detergent cleansers with or without moisturizing substances reduced the incidence of skin tears, incontinence-associated dermatitis, and superficial pressure ulcers (Kottner et al. 2013).

Cleansers in Different Dermatologic Conditions

Acne

Acne is a common skin disease that involves the seborrheic area of the face and results from the obstruction of hair follicles followed by inflammation. Face washing is indispensable for acne therapy, because discontinuation of cleansing exacerbates acne (Isoda et al. 2015a).

For severe cases, medications, including systemic and topical antimicrobials and retinoids, have been used as prescribed drugs. Careful face washing improves the lesions and prevents acne development by removing excess sebum and preventing hair follicular obstruction (Isoda et al. 2015a). There is a wide spectrum of skin cleansing agents for acne-prone patients, ranging from lipid-free cleansers, syndets, astringents, exfoliants, and abrasives. Natural soaps should be avoided because of the irritation potential and the risk of leaving residues that may induce the formation of comedones (Mukhopadhyay 2011).

Intensive face washing has a risk of inducing skin barrier impairment and dry skin. Many acne subjects worry about their dry skin and also have sensitive skin (Isoda et al. 2015a).

The major pathogenic factors of acne are obstruction of hair follicles, abnormal keratinization of hair follicles, abnormal sebum metabolism, sebaceous hyperproliferation, increased numbers of microbes especially *Propionibacterium acnes* (*P. acnes*), and/or inflammation. The basic therapeutic strategies for acne care are the control of sebum secretion, abnormal cornification of keratinocytes in hair follicles, and bactericidal agents. Therefore, anti-inflammatory agents, bactericidal agents, and keratinization control agents have been used for acne care (Isoda et al. 2015b).

Many people are concerned that washing the face with a product with high sebum-cleansing ability may induce skin problems, such as dry xerotic skin. Thus, effective facial cleansers for acne therapy must satisfy two conflicting needs, that is, removal of sebum and maintaining skin moisture (Isoda et al. 2015b). The addition of emollients to liquid cleansers prevents and relieves irritation as a result of treatments for acne, and it is important even in patients with oily skin.

The major side effects of most anti-acne therapies are skin dryness and irritation, so gentle cleansing is important for this group of patients.

The myth associated with acne that vigorous skin scrubbing with soap and water several times a day will reduce the amount of oil, however, only leads to an aggravation of acne, and sometimes it even may cause acne detergicans (Mukhopadhyay 2011).

Choi et al. 2006 assessed the frequency of face washing in cases of acne vulgaris and recommended washing the face twice daily with a mild cleanser. Dermatologists often warn that overwashing and excessive scrubbing can irritate and exacerbate the condition.

The efficacy of skin cleansers containing anti-acne reagents or antibacterial reagents has been assessed in acne therapy.

There is an ethnic variation in androgen productivity. Asians produce less androgen than Europeans and have less oily skin with less sebum production. The acne severity in Japanese patients is milder than that of European ones.

A nonionic, fragrance-free dermatologic bar or liquid cleanser with good rinsability is the recommended cleanser for acne cases. The cleansing regimen should suit the needs of the individual patient (Mukhopadhyay 2011).

Rosacea

The skin of patients with rosacea is extremely sensitive to chemical irritants. The skin hyperreactivity seen in patients with rosacea warrants careful selection of any skin care products, especially cleansers, because they are the most frequent topical cause of barrier damage (Draelos 2004; Mukhopadhyay 2011).

Facial rosacea is also associated with an overly permeable skin barrier, and as a result, these individuals have a lower tolerance to many skin care products and cosmetics (Draelos et al. 2013).

Rosacea also has been characterized as a disorder of the stratum corneum barrier, allowing irritants to affect the viable epidermis and dermis causing vasodilation, flushing, and inflammation (Isoda et al. 2015a, b). As previously noted, individuals with various subtypes of rosacea are exquisitely sensitive to numerous environmental factors; both irritant and allergic contact skin reactions are more common in patients with rosacea than in individuals with normal skin (Draelos 2004). The choice of cleanser is also important. It is recommended to avoid the traditional soaps, products containing alcohol, astringents, and abrasives. It is recommended to use gentle cleansing agents or cleansers with active therapeutic action, such as sulfacetamide and sulfur. Vigorous cleansing should be avoided. Gentle cleansing is recommended in rosacea patients (Mukhopadhyay 2011).

Patients with ocular rosacea may have blepharitis, and in this case, eyelid daily hygiene is extremely important to control the situation. The care of rosacea patient should include face washing with warm water, should avoid using sponges or similar material, and should wait at least 30 min after washing to apply topical products for treatment.

Atopic Dermatitis

Atopic dermatitis (AD) develops as a result of a complex interrelationship between environmental, immunological, genetic, and pharmacological factors (Mukhopadhyay 2011). In individuals with atopic dermatitis, the use of a cleanser with traditional surfactants can exacerbate the disease, leading to loss of intracellular lipids and the skin with a red, scaly appearance. Further, skin damage to those with AD can lead to exposure of dermal nerve endings, resulting in itching, burning, and pain. Most guidelines for AD treatment stress the importance of basic skin care such as proper application of moisturizers and bathing/showers. AD patients should bathe using mildly acidic soaps once daily, for several minutes in warm water, and immediately apply emollients after bathing. Bath additives such as oils can be added to the water to reduce transepidermal water loss. Epidermal barrier impairment in AD patients can contribute to the penetration of allergens and antigens through the skin. This damage to the skin barrier function could result in increased colonization of gram-positive bacteria. Mild syndets with an adjusted pH value (acidified to pH 5.5–6.0) should be used for cleansing, because the use of neutral-to-alkaline soaps can lead to the precipitation of AD through barrier-dependent increases in pH and serine protease activity. Therefore, regular showers using weakly acidic pH soaps might be beneficial for the practical management of AD by removing infectious organisms, irritants, or allergens (Kim et al. 2012). Daily bathing using weakly acidic syndets with immediate application of an emollient can reduce skin symptoms in patients with AD.

Bath care is part of the treatment of atopic dermatitis. It is recommended to avoid soaps due to potential irritation and give preference to soft synthetic cleansers. Cleansers enriched with fats can be beneficial, as they reduce the depletion of skin lipids by acting as a sacrificial lipid, and also in the micelles deposited on the skin during washing, which, moreover, are identified as a possible cause of eczema trigger, this residue also contains surfactants.

Eczemas

Cleansers can cause contact dermatitis by primary irritation, allergic, phototoxic, or photoallergic. Prevention is the key to reduce the incidence and prevalence of contact dermatitis. Individuals suffering from these disorders should practice good skin care daily. Avoidance of causative irritants both at home and the workplace is the primary treatment of contact dermatitis. The most common occupational skin disease in the industrialized world is hand dermatitis. Frequent hand washing can cause contact dermatitis by primary irritant, which is usually caused by surfactants. Skin-compatible hand cleansing is vital for the prevention of hand dermatitis (Mukhopadhyay 2011; Biasi 2012; Gunathilake et al. 2007).

Wet work professionals are at high risk of developing contact dermatitis from frequent contact of the skin with irritants in aqueous solution. The incidence of irritant contact dermatitis exceeds that of allergic contact dermatitis. Their occurrence is frequent in wet work professionals as housekeepers, professional cleaners, and health workers by frequent exposure to water, soaps, and detergents (Gunathilake et al. 2007; Mukhopadhyay 2011).

Health workers must repeatedly wash and disinfect their hands for hygienic reasons. Increased stratum corneum hydration allows additional permeability of potential irritants: after 4 h of experimental water exposure, the stratum corneum on the ventral aspect of the lower arm increases up to threefold. Furthermore, soaps, surfactants, and detergents facilitate penetration, and some are potential irritants themselves (Mukhopadhyay 2011; Gunathilake et al. 2007).

The continuous usage of soap or an alkaline cleanser may increase the skin surface pH. An alkaline pH could perturb epidermal barrier function, due to the deleterious effects of an elevated pH on the barrier. A pH of 4.5–5.5 is required for optimal barrier function and repair. Maintenance of an acidic pH to prevent occupational skin diseases, particularly with respect to the hand, is challenged by repeated hand washes using an alkaline soap (Takagi et al. 2015; Gunathilake et al. 2007).

While liquid synthetic detergents are generally perfectly adequate for cleansing hands at home, more powerful hand cleansers are needed for the removal of heavy-duty industrial soiling such as oil, grease, paints, and lacquer. The basic requirements for an efficient skin cleanser to prevent occupational skin diseases are its easy solubility in both hard and soft water; its ability to remove fats, oils, and greasy materials without drying the skin; its free flow through the dispensers; and a long shelf life without easy deterioration on storage. In reality, however no cleanser can be labeled as ideal for occupational dermatosis (Mukhopadhyay 2011; Biasi 2012).

The choice of cleanser in such cases should strike a balance between protecting the skin and be effective in removing industrial waste oils and greases. Although numerous studies have evaluated the antimicrobial efficacy of different hand decontamination measures, their simultaneous impact on barrier function has not been assessed. Products free from scrubbing agents are usually skin friendly and preferred by dermatologists (Mukhopadhyay 2011; Biasi 2012; Gunathilake et al. 2007).

Take-Home Messages

Selecting the proper cleanser is key to maintaining the skin acid mantle and preserving skin health.

Surfactants enable the solubilization of oils, dirt, sebum, and other unwanted substances from the skin, allowing these materials to be washed away.

The cleanser's pH may contribute to damage the stratum corneum.

Traditional soaps are alkaline in nature and are thought to impair the lipid bilayer of the stratum corneum barrier.

Synthetic detergent cleansers (syndets) are formulated to have a neutral (7.0) or slightly acidic pH to ensure skin compatibility.

Cross-References

- ▶ Approach in Photodamaged Skin, Melasma, Acne, and Rosacea
- ▶ Evaluation and Classification of Aging
- ▶ Skin Anatomy, Histology, and Physiology

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Retinoids

David Rubem Azulay and Dâmia Leal Vendramini

Abstract

Retinoid includes all natural or synthetic compounds based in vitamin A (Vit. A) similar activity, thereby has the ability to activate nuclear retinoid receptors. Through the discovery of nuclear receptors for retinoic acid, greater understanding of mechanism of action of these compounds was achieved. Such advance allows also the possibility of development of molecules with specific roles in various pathological affections that are the cause of many diseases.

These receptors are coupled to certain regions of DNA that are responsive to activation by retinol and/or retinoic acid. Subsequently, the message is transcribed (messenger RNA) to ribosomes, where proteins are synthesized. Therefore, they end up acting at the cellular differentiation, embryonic morphogenesis, and carcinogenesis.

Retinoids are classified into generations. The first generation: retinoic acid (RA), tretinoin or acid vitamin A, alitretinoin (9 *cis*-retinoic acid), and isotretinoin (13 *cis*-retinoic acid). They are all isomers and naturally occur in the organism.

Acitretin and its precursor etretinate are the second-generation retinoids.

The more recent third generation is represented by adapalene, tazarotene, motretinide, and arotinoides.

Retinoids have a large number of indications. According to the indication, their use can be topical or systemic. Their benefits range from anti-inflammatory action, immunomodulatory effects, and more recently of photoaging.

A huge list of possible adverse effects must be known in order to minimize the risk. They are essentially dose dependent.

Keywords

Retinoids • Retinoic acid • Tretinoin • Vitamin A • 9 *cis*-retinoic acid • Acitretin

Contents

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Introduction

The current definition of retinoid includes all natural or synthetic compounds with vitamin A (Vit. A) similar activity; so they have the ability to activate nuclear retinoid receptors. Vit. A in humans encompasses several interconverting compounds, of which the main ones are retinal (essential for vision) and retinol (an analogue more potent, essential to reproduction, besides that, it represents the transportation and liver storage forms). Embryonic growth, morphogenesis, differentiation, and maintenance of epithelial tissues are other functions inherent to this vitamin (Nguyen et al. 2001).

Vit. A is necessarily obtained from an exogenous source. Retinyl ester forms may be obtained through the ingestion of carotene, especially the beta-carotene, contained in plant and animal products such as meat, milk, and eggs. Already in the intestinal lumen, retinyl esters are converted after hydroxylation in retinol, allowing absorption and storage in the liver, mainly in the ester form.

Since 1920, it was known that Vit. A-free diet induces epithelial metaplasia and, if suspended, occurred reversal of the process, if maintained evolved to gastric epithelial neoplasia. Due to this observation, the initial idea of using retinoids was as antineoplastic drugs.

In 1987, through the discovery of nuclear receptors for retinoic acid, the mechanism of action of these compounds was better understood. Such advance allowed the development of new molecules with specific roles in various pathogenetic pathways that are the cause of many diseases (Armstrong et al. 1992).

Classification of Retinoids

Retinoids are classified into generations (Fig. 1).

First Generation

The first generation is represented by retinoic acid (RA), tretinoin or acid vitamin A, alitretinoin (9 *cis*-retinoic acid), and isotretinoin (13 *cis*-retinoic acid) (Nguyen et al. 2001).

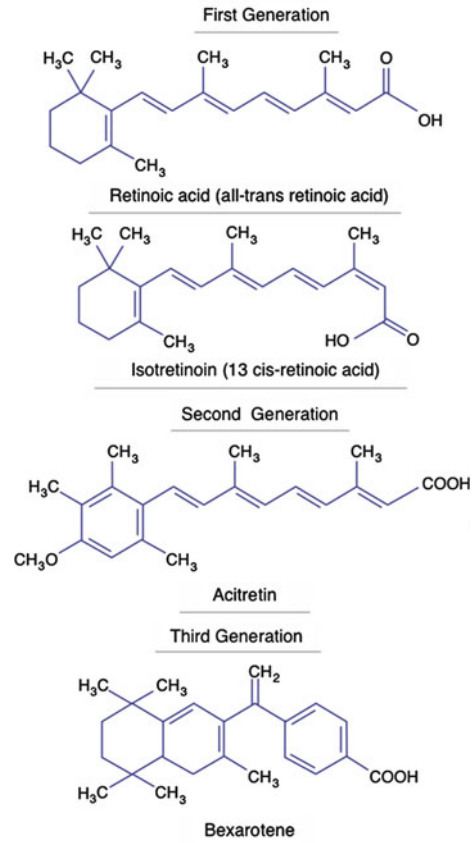

Fig. 1 Representation of the molecular structures of retinoids in their different classes

They are all isomers (same chemical composition but different spatial configuration) and naturally occur in the organism.

The low therapeutic index (TI = efficacy/toxicity) of RA in keratinization diseases and acne turned to be quite worthless for their clinical treatment. By having better TI, isotretinoin has been used for many years with great success in the treatment of these affections. Alitretinoin has been used topically and in capsules for the treatment of Kaposi's sarcoma, AIDS, and chronic eczema of the hands.

The RA can be applied topically and systemically. As a systemic drug, it has an effective action in the treatment of acute promyelocytic leukemia blocking the long-arm translocation of the chromosome 17 to 15.

Second Generation

Etretinate and acitretin are the second-generation retinoids. Both are monoaromatic retinoids, obtained by combining an aromatic ring, associated with the replacement or not of the vitamin A terminal cyclic grouping (Nguyen et al. 2001). It has been withdrawn from the market due to its long half-life of 120 days; characteristically lipophilic, it accumulates for long periods in the adipose tissue. Due to its teratogenicity, pregnancy has to be avoid for up to 3 years after the intake of the last dose.

Acitretin is the major metabolite of etretinate after losing the carboxylic acid radical. This change makes it more soluble, with a 2-day half-life. It should be noted that in obese individuals and alcohol abusers, acitretin converts to etretinate. Therefore, even with less potential teratogenicity, the 3-year contraceptive measures need to be sustained. The TI is similar between the two compounds.

Third Generation

The more recent group of the third generation is represented by bexarotene, adapalene, tazarotene, motretinide, and arotinoides. They are polyaromatic retinoids resulting from the cyclization of the polyenic side chain. Some have only similar retinoid action (adapalene and tazarotene), but no longer structurally similarity to vitamin A. Bexarotene is already approved for use in the systemic treatment of recalcitrant cutaneous T-cell lymphoma (CTCL). Some arotinoides are about 1,000 times more potent than the other retinoids, but TI is not higher, except for glucuronide derivatives (Nguyen et al. 2001).

A new class of compounds known as blocking agents of the metabolism of RA (rambazole and liarozole) has been tested. The action is essentially the blockage of CYP 26 enzyme (4-retinoic acid hydroxylase), which prevents oxidative degradation of the RA and thus, increases tissue levels of RA (Sardana et al. 2003).

Systemic Retinoids

Pharmacokinetics

The absorption of retinoids is increased by up to 50% when taken with food. Once in the blood flow, retinoids are transported associated with plasma proteins (retinol-binding protein (RBP) and transthyretin). The metabolization is in the liver, through the cytochromes P450, 3A4, and 26 (Petkovich 2001).

Irreversible metabolism of retinoic acid and its isomers occur through oxidation, respectively, into 4-oxo-retinoic acid, 4-oxo-9-*cis*-retinoic acid, and 4-oxo-isotretinoin, which also are capable to interconvert among them. During the treatment with isotretinoin, 4-oxo-isotretinoin is found at a concentration of five to six times higher than the natural level of isotretinoin, and they are the real sebostatic retinoids (Petkovich 2001; Rabello-Fonseca et al. 2006).

Acitretin metabolism begins with the formation of isomer 13-*cis*-acitretin, and both are subsequently transformed by demethoxylation of the aromatic ring and finally excreted of as β-glucuronide.

Excretion of all retinoids is done primarily through the bile and urine (Table 1).

Pharmacodynamics

On the membrane cells, the retinoids bind to surface receptors and penetrate into the cells. Once inside them they are metabolized and transported to the nucleus by cytosolic proteins. The CRBP (cytosolic retinol-binding protein) modulates the process by which the retinol undergoes through oxidation and becomes reversibly in retinaldehyde, then irreversibly in RA. In RA form, it is transported to the nucleus by enzymes called CRABP-I and CRABP -II (cytosolic retinoic acid-binding protein), which also modulates the quantity of free RA in the cell. The CRABP-II is the predominant protein in the human epidermis; its expression increases with epithelial differentiation, and retinoids, in contrast, reduces its expression (Dong et al. 1999).

Table 1 Pharmacokinetics

	Absorption and transport			Elimination	
	Peak serum	Protein	Half-life	Metabolism	Excretion
Tretinoin	1–2 h	Albumin	48 min	Hepatic	Bile, urine
Isotretinoin	3 h	Albumin	20 h	Hepatic	Bile, urine
Etretinate	4 h	Albumin	120 days	Hepatic	Bile, urine
Acitretin	4 h	Albumin	2 days	Hepatic	Bile, urine
Bexarotene	2 h	Plasma protein	7 h	Hepatic	Bile

The RA is the main intracellular retinoid and its major isomer, 9-*cis*-retinoic acid, (alitretinoin) has specific receptors; on the other hand, 13-*cis*-retinoic acid (isotretinoin) doesn't have specific receptor.

Those receptors are called the RAR and RXR receptors. The X denomination was due to the initial lack of knowledge of what would be later the receptor for the 9-*cis* retinoic acid. These receptors are part of the superfamily of receptors found in almost all animals, which act as DNA transcription factors, as it happens with the receptors for cortisol, vitamin D, and thyroid hormone (Kang et al. 1997).

These two receptors act as heterodimers, combining a RXR and RAR, or as RXR dimers or even like a RXR heterodimer along with other nuclear receptors such as the thyroid, vitamin D, and activated proliferator peroxisome receptors. The RXR and RAR receptors have three subtypes, named "α," "β," and "ý," which are synthesized by different genes. The most commonly found in the epidermis are RAR-ý and RXR-α. RAR-β is predominantly found in the dermis. The RAR-β is more related to annex final differentiation, while the main receptor associated with teratogenicity is RAR-α that is omnipresent and also relates to keratinocyte proliferation. Bexarotene, by only activating RXRs, is a prototype of "rexinoid" (Elmazar et al. 1996).

These receptors are coupled to certain regions of the DNA (retinoic acid-responsive elements) that are responsive to activation by retinol and/or retinoic acid. Subsequently the message is transcribed (messenger RNA) to the ribosomes, where proteins are synthesized. Once the proteins are formed, they follow both paths: be structural or return to nucleus, enabling its action as agonists, antagonists, or be neutral in various immunological and inflammatory processes, in oncogenesis, on apoptosis, and the production of cytokeratins, growth factors, sebum, collagen matrix, and among others. Therefore, they end up acting in cellular differentiation, embryonic morphogenesis, and carcinogenesis. The activation of these proteins in other genes determines the so-called amplification of the response or gene expression.

The discovery of nuclear receptors for RA represented a great advance in the study of the retinoids and will enable design molecules with higher specificity, better therapeutic index, and mainly without teratogenicity.

Indication

Retinoic Acid

The oral presentation is indicated for the treatment of acute promyelocytic leukemia. The participation of *P. acnes* in the activation of toll-like receptors 2 with the release of inflammatory cytokines is a relevant aspect in acne pathogenesis (Liu et al. 2005). Recently the anti-inflammatory and immunomodulatory actions of retinoic acid and adapalene, applied topically, have shown decreased expression of these receptors in human monocyte membranes.

Isotretinoin

Due to its sebostatic action, is indicated in acne vulgaris – precisely on nodulocystic acne, recalcitrant, especially on those patients predisposed to scarring. Its effectiveness is so great that it became to be the gold standard treatment for acne. Off-label indications include less severe forms of acne, considering the psychological status of the

patient and those acnes with solid facial edema. It is also indicated in the treatment of other follicular disorders, such as gram-negative folliculitis, HIV-associated eosinophilic folliculitis, rosacea (papulopustular and in granulomatous forms), dissecans scalp folliculitis, and suppurative hidradenitis, the last one with unsatisfactory results. It also has great effect as treatment for keratinization disorders, especially in Darier's disease as well as in other diseases, but, in general, has much more long-term side effects than acitretin, mainly over the bone structure (Ellis et al. 2001).

Isotretinoin has been used in low doses (1–3 weekly capsules) for the treatment of photoaging. Should think about the benefit once the long-term use may cause incalculable risk of osteopenia/osteoporosis. This risk is higher after menopause because metabolism is significantly slower (Rabello-Fonseca et al. 2009).

Some authors defend its use in psoriasis (considering women of childbearing age), with lower efficacy than acitretin, but better in terms of allowing pregnancy in a shorter period of time after discontinued. It can be associated with PUVA with an increased response.

Acitretin

It is an FDA-approved treatment for psoriasis, indicated by many guidelines, classically in pustular or erythrodermic forms, although this drug can benefit recalcitrant and severe psoriasis plaque (Katz et al. 1999).

Acitretin also has great action in keratinization diseases such as Darier's disease, pityriasis rubra pilaris, ichthyosis, and keratodermas. In epidermolytic keratodermas and ichthyosis (ichthyosiform erythroderma congenital bullous), it is recommended to start with low doses, because otherwise, will lead to the emergence of large erosions.

It has been used as chemoprophylaxis in several diseases with high risk of cutaneous cancers, such as xeroderma pigmentosum, the basal cell carcinoma syndrome (Gorlin-Goltz), Muir-Torre syndrome, and epidermodysplasia verruciformis. Similarly, immunocompromised patients (primary or especially secondary) have a tendency to trigger mainly squamous but also basal cell carcinoma, as well as increase the number of them (Bavinck et al. 1995; DiGiovanna 1992).

Bowen's disease, leukoplakia, and severe cheilitis have benefited from treatment continued at a dose of 30 mg/day. Isotretinoin has similar efficacy in these situations.

Other unusual indications are lupus erythematosus, lichen planus, lichen sclerosus et atrophicus, graft-versus-host disease, and even infections triggered by HPV.

Bexarotene

It is approved for the systemic treatment of unresponsive/nonresponsive cutaneous T-cell lymphoma (CTCL) to at least one previous treatment.

Alitretinoin

Hand eczema that not responded to prior usual therapy represents an approved indication for alitretinoin (Ruzicka et al. 2008).

Contraindications

Absolute

- Pregnancy or childbearing women without effective contraceptive methods
- Breastfeeding
- Hypersensitivity to parabens (isotretinoin in capsules)
- Unstable or unreliable patient
- Patient who underwent myopia laser surgery less than 6 months before (Miles 2006)

Relative

- Leukopenia
- Hypothyroidism (for patients with bexarotene indication)
- Dyslipidemia
- Liver and renal dysfunctions

Teratogenicity

Retinoids are absolutely contraindicated in pregnancy (FDA category X) and lactation. Teratogenicity occurs in about 20–40% of pregnancies at term, as well as miscarriage in approximately 33%

of pregnancies. Most of the data is related to isotretinoin, probably due to its indication in female patients with acne (Jick 1998).

The main manifestations are so classic that are called retinoid embryopathy: central nervous system (hydrocephalus, cortical alterations, microcephaly, cerebellar agenesis), cardiovascular system (septal defects in the atrium and ventricle, aortic malformation), eyes (microphthalmia and optic nerve atrophy), ear (microtia, absence of the ear canal, deafness, vestibular dysfunction, etc.), craniofacial abnormalities (jaw malformation, cleft palate, anencephaly, and various bone changes), and thymic hypoplasia or aplasia.

The period of posttreatment contraception for isotretinoin, tretinoin, and bexarotene is 1 month and for acitretin is 3 years in the United States and two in Europe.

Some important notes about the use of retinoid are:

- Although all patients and their direct guadian or parents (if under 18-years-old) sign the post-informed consent, this does not exempt the doctor, from a legal point of view, of a lawsuit in Brazil.
- Scientifically, retinoids are not mutagenic nor affect spermatogenesis; however, it is recommended for men to avoid conception during treatment.
- Blood donation is contraindicated.

Laboratory Abnormalities

Before initiating a systemic retinoid treatment, female patient must have a negative β-HCG, and male and female patients must present lab tests (mentioned ahead) within the normal range.

Laboratory tests should be collected before treatment and repeated after 3 weeks of isotretinoin intake and then monthly till the end of the treatment. Similarly, for acitretin and bexarotene, a test before treatment and then repeated 2 or 3 months after the beginning, followed by laboratory evaluation every 3 months, is advisable. The timing for the lab tests is adjusted individually, according to every patient scenario.

Except for teratogenicity, most of the changes are essentially dose dependent, and therefore a dosage reduction might be sufficient. Dietary habits, especially alcohol restriction, along with moderate reduction on exercises are helpful.

Laboratory routine tests include β -HCG, complete blood count, AST, ALT, alkaline phosphatase, ý GT, blood glucose, cholesterol, triglycerides, CPK, urea, creatinine; T_3, T_4, and TSH (bexarotene), and EAS.

Treatment with Systemic Retinoids

They must be taken with food, because its absorption is increased by 50% and preferentially fractionated in two doses, in the case of isotretinoin. Systemic use, regardless of the disease, does not invalidate adjuvant topical therapy. Usually, acitretin has slightly higher efficacy than isotretinoin in keratinization disorders, except Darier's disease and seems to be less long-term toxic.

The use of lip moisturizing is mandatory, especially those that are taking isotretinoin due to cheilitis that occurs in about 100% of the patients.

Isotretinoin

It is very effective in the acne treatment. The mechanism of action is related to correction of keratinization disorder with thinning of the stratum corneum, decreased adhesion of keratinocytes, temporary atrophy of the sebaceous glands, and decreasing the chemotaxis of neutrophils, also modifying the sebum composition due to the lower conversion of triglycerides.

Lower doses are just a little bit inferior in terms of efficacy with the benefit of being lesser toxic, but recurrence rates are much higher. Recommended dose should be between 0.5 and 1 mg/kg/day to achieve a total dose of 120 mg/kg in little more than 5 months. Evidences support that when a total dose of 120–150 mg/kg is reached, the chance of recurrence becomes less likely. Acne in the trunk generally requires longer treatment and higher dose (Ellis et al. 2001).

Around 20% of the patients will require new treatment cycle, and even a greater number of

patients will still depend on topical therapy to maintain control. Recurrences rates are higher in those with severe forms of acne, especially in younger patients. Women with hormonal disorders certainly present relapse too.

There might be an initial worsening of acne between 2 and 8 weeks, called flare-up, particularly in male patients under 16 years who have closed comedones and for those who use doses higher than 0.5 mg/kg/weight.

Chemical or mechanical peelings are contraindicated during and for at least 6 months after treatment with isotretinoin.

In Brazil it is marketed in 10 or 20 mg capsules.

Acitretin

It is extremely effective in treating various skin diseases: psoriasis, Darier's disease, pityriasis rubra pilaris, ichthyosis, palmoplantar keratoderma, and among others. A clinical response, as well as the toxicity, is dose dependent (Katz et al. 1999).

The therapeutic response in different forms of psoriasis can be considered good to excellent, with the best results on pustular and erythrodermic forms. It is also effective in psoriasis set off by HIV infection.

The total initial dose should be between 20 and 30 mg, tapering every 2–3 weeks according to its response and eventual toxicity. The dose may reach 0.75 mg/kg/day. In psoriasis, high doses since the beginning may be associated with an initial worsening of erythema or even spread the disease (Katz et al. 1999).

Association with methotrexate can increase efficacy but also can enhance hepatotoxicity. Other option to improve the outcome is RePUVA method (PUVA associated with acitretin).

Recurrence usually does not occur at the end of therapy.

The presentation of acitretin is in 10 and 25 mg capsules.

Bexarotene

It is indicated for the treatment of cutaneous T-cell lymphoma (CTCL), unresponsive to at least one systemic therapy. The best results are seen when used in plaque stage. The response occurs in 50–60% of cases within 2 months.

Bexarotene can trigger hypothyroidism; therefore, it is necessary to periodically evaluate TSH and T_4. It also and can be myelotoxic, requiring close follow-up.

The drug is available at a dose of 75 mg per capsule. The initial proposed dosage is 300 mg/m^2/day and administered on single daily dose. The dosage should be adjusted according to the efficacy and toxicity.

Retinoic Acid

Retinoic acid is use in hematology for the treatment of acute promyelocytic leukemia. There are no current indications on dermatological diseases, even though it should be known by dermatologists due to its cutaneous side effects

Retinoic acid syndrome, which is potentially fatal, is characterized by fever, breathlessness, generalized edema, including pleural and pericardial effusion, and hypotension (Frankel et al. 1992). It usually occurs about 3 weeks after the beginning of the treatment. Along with that, some cases of ulceration of the scrotum and tongue have been described (Riganti et al. 2014). Also should be remembered as one of the causes of systemic capillary leak syndrome or leak syndrome as well as can be triggered by erythrodermic or even pustular forms of psoriasis (Bressan et al. 2011).

In the remission of the leukemia may occur in Sweet's syndrome. The dose used is 45 mg/m^2/day. The presentation is in 20 mg capsules.

Drug Interactions

The substances that increase the plasma level or toxicity of retinoids are vitamin A, tetracyclines, gemfibrozil (bexarotene), macrolides, and azoles, and those that may decrease the plasmat concentrations of retinoids are rifampicin, rifabutin, phenytoin, phenobarbital, and carbamazepine via CYP 3A4 and can increase the plasma level of cyclosporin via CYP 3A4.

Acitretin can decrease the level of progesterone on contraceptives (minipill) (Berbis et al. 1988).

Other important interactions are alcohol and methotrexate, due to the hepatotoxicity.

Exceptionally, there may be an interaction of systemic retinoids with topical retinoids. The association can be used in the beginning of the treatment prescribing daily or a every other night topical retinoids according to the level of retinoid skin irritation.

Side Effects

There are numbers of side effects, and they are essentially dose dependent, except for the teratogenicity, which is the most worrying problem. The majority of the patients will present side effects with oral medication, which may be clinical and/or laboratorial.

Considering the clinical indications and the time of use, the treatment of acne with isotretinoin is quite safe, as expected reversal of all side effects after the end of treatment. The use of acitretin, due to the chronic nature of the disease to be treated, can leave some irreversible consequences, but it is the only therapeutic option for certain disfiguring diseases such as ichthyosis, which has no previous effective therapy. It is an extremely effective class of drugs that should be prescribed after conscious assessment of the risk/benefit.

Teratogenicity

It is always recommended to use two contraceptive methods. Treatment should only be started after a period and with a negative pregnancy test. Untrusted patients should not receive treatment (items contraindications and drug interactions, above) (Jick 1998).

Mucocutaneous Effects

Cheilitis occurs in a 100% of patients using isotretinoin and can be used as a marker to see if the patient is actually taking the medication. The skin becomes xerotic, thin, and fragile in about 80% of cases, predisposing infections by *Staphylococcus aureus*. This is called retinoid dermatitis, which also makes the skin more sensitive to radiation, and it is dose dependent. It must be advised to avoid intense sun exposure and to use of sunscreen; the retinoid dermatitis should not be mistaken with an authentic photosensitivity.

Peeling of the palms and/or plants occurs most often with acitretin. Nasal dryness with epistaxis (about 20%), oral, and ocular are common.

Exuberant granulation tissue can occur in the most inflamed acne lesions, especially on the trunk, and acitretin typically triggers in the corner of the nails; we have described one case report of a conjunctival area with acitretin (Azulay et al. 1985; Raso et al. 2008).

Unusual cases of pyoderma gangrenosum are associated with isotretinoin.

Some cases of urticaria (probably due to the capsule of paraben), erythema nodosum, and erythema multiforme have been described.

Nails can become fragile, with onychorrhexis and onychoschizia. Onycholysis also may occur. These changes are more frequent with acitretin as well as the telogen effluvium. In general, it regresses after the end of the therapy or with a significant dose reduction.

Hematuria due to changes of the mucosa may occur and it is more related to acitretin.

Bone Changes

There are numerous bone changes, and they tend to occur especially with higher doses and in long-term treatments and pain can occur without radiological changes. Osteoporosis, ligament and tendon calcifications (especially the ankles), periosteal thickness, premature closure of the epiphysis, remodeling of long bones, and cortical hyperostosis (diffuse idiopathic skeletal hyperostosis (DISH)) are described as possible adverse effects. The development of osteophytes during treatment can be a manifestation of DISH and, when severe, with involvement of the posterior ligaments, can lead to a severe spinal cord compression that may require surgery. Generally, the typical ligament calcification in DISH is asymptomatic. Long-term treatments, according to the therapeutic plan, deserve a pretherapeutic and an annual radiological evaluation (DiGiovanna 2001).

Ocular Changes

Blepharoconjunctivitis occurs frequently; however, staphylococcal conjunctivitis occurs only in 7% of cases (colonization conjunctival sac

reaches 62% of patients). The author's opinion is that the published data do not match to the higher incidence at the clinical practice. The use of eye drops helps to improve the symptoms. Patients who wear contact lenses should be advised about the risk of complications. Corneal erosions rarely occur. Visual disturbance, with severe headache, may be the foretaste of pseudotumor cerebri (see below). The loss of night vision is uncommon as well as the difficulty to distinguish between colors, due to the decreased rhodopsin formation.

Liver Changes

Change of the AST and ALT levels occur in approximately 15–20% of the patients, but real hepatitis is uncommon and may therefore need a reduced dosage or an interruption of the treatment. There are exceptional cases of fulminant hepatitis. Immediate suspension should be adopted when elevation is higher than three times compared to the baseline. It is recommended to avoid alcohol also by the lipid alterations. Nonspecific gastrointestinal disturbances are occasionally reported.

Lipid Metabolism

It is common to identify plasma lipid level changes, occurring in almost 50% of patients (triglycerides 50% and cholesterol 30%) using acitretin and isotretinoin and in 70% using bexarotene. Some authors suggest associating atorvastatin for patients using bexarotene (item interactions, above). Avoiding alcohol and instituting dietary control may be sufficient measures to correct the dyslipidemia. When triglyceride levels exceed 500 mg/dL or cholesterol over 250 mg/dL, the discontinuation of the treatment should be advised.

Pancreatitis

Pancreatitis is a rare side effect, but potentially fatal and usually results of a secondary dyslipidemia (increase in triglycerides above 770 mg/dL). It occurs most frequently in bexarotene users.

Neuropsychiatric Disorders

Although most case reports of pseudotumor cerebri have being related to a concomitant use of antibiotics (specifically with the tetracycline family), retinoids can by itself unleash it. Severe headache, nausea, vomiting, and papilledema are the manifestations that should point to a pseudotumor diagnosis. Discrete and transient headache is frequent at the initial period of treatment (Lee 1995).

About behavioral changes, it is controversial and difficult to distinguish if, in fact, it is related to the use of isotretinoin itself or due to the basic dermatological condition. If we consider the number of reported suicides of over millions users, it is found a number of five to six times lower than in the general population. Depression occurs in about 17% of young people. Particularly the authors are not convinced about this linkage. However, it is possible that someone can use acne as an excuse to justify his or her difficulties in social-affective relationships and may get depressed after the cure of the disease. Every patient deserves a careful attention, and if manifestations of depression are identified, the doctor should strengthen and improve the patient's relationship and, if not sufficient, refer him to a psychiatrist (Jacobs et al. 2001; Marqueling et al. 2005, 2007).

Musculoskeletal System

Myalgia occurs in 15% of the patients in use of isotretinoin and rarely with acitretin. CPK elevation certainly occurs in patients who have maintained intense physical activity, and, therefore, patients should be recommended to decrease it during treatment.

Thyroid Disorders

It occurs in 40% of bexarotene users and is characterized by an increase of TSH levels and T_4 reduction.

Hematologic changes

Hematologic changes are not important or even frequent, but they occur mainly in patients using bexarotene (leukopenia occurs in 28% of patients).

Topical Retinoids

Tested initially for the treatment of keratinization disorders, retinoic acid was first used for the treatment of acne in 1969, its photoaging and

antiaging proprieties were observed about 20 years ago. Other topical retinoids are adapalene (acne and photoaging), isotretinoin (acne, photoaging), tazarotene (psoriasis and acne), and alitretinoin (Kaposi's sarcoma).

Topical retinoids can be formulated with cream or gel vehicles for the treatment of acne and for antiaging and photoaging are associated with emollients.

Retinoid dermatitis is the main side effect of retinoic acid and consists of irritation characterized by erythema, desquamation, burning, and/or itching. It happens so often that patients must be instructed to reduce the frequency or amount of substance applied if these effects are intense. Most patients have photosensitivity and should be oriented to avoid the sun and to use sunscreens.

Usually, retinoids are photolabile and hence should only be applied at night. Some trials have shown their effectiveness for the treatment of preneoplastic lesions. Although it is unlikely that the topical use causes teratogenicity, it is contraindicated in pregnancy.

The effects of retinoic acid can already be noted after few months of use in histopathological slides of photoaging skin and consist of atrophy being replaced by epithelial hyperplasia, increased collagen production, and angiogenesis. There is also a greater uniformity of melanin granule distribution, destruction of microscopic actinic keratoses, and clinically visible improvement of the fine wrinkles. It is also indicated for the treatment of striae distensae and for it's improvement used in higher concentrations (0.1%) aiming the stimulation of collagen synthesis by inhibition of collagenase.

Retinoic acid (vitamin A acid or tretinoin) is found in the market at concentrations of 0.25% and 0.05% in gel or cream at concentrations of 0.025%, 0.05%, and 0.1%. It can be manipulated, and it is frequently recommended in a 0.05% solution for the treatment of acne on the trunk.

Adapalene is extremely effective for the treatment of acne and is less irritating and photosensitizing. They are produced at a concentration of 0.1% cream or gel and more recently 0.3% gel, and it is also used for the treatment of photoaging. Another new formulation launched is the association of adapalene 0.1% and benzoyl peroxide 2.5%, with great effectiveness.

Isotretinoin is also extremely effective in acne treatment, being much less irritating than retinoic acid. It is available at the concentrations of 0.025–0.05% gel or cream.

Tazarotene 0.05 or 0.1% cream is the first topical retinoid for psoriasis, although it is also useful for the treatment of acne. It is indicated for patients that has up to 20% of the body surface compromised. It should be applied once a day. Side effects occur in about 10–30% of the patients, and they can complain about itching, burning sensation, redness, irritation, scaling, xeroderma, worsening of the psoriasis, and local pain. Pregnancy is an absolute contraindication, so women, and women should be advised to adopt effective contraceptive measures. Photosensitizing drugs should be avoided as they might enhance photosensitization. It has been recommended its association with medium-potency steroids, once a day. In this case, there is an improvement of 50% or more on the doctor's evaluation and 90% in the patient's opinion at the end of 12 weeks of treatment.

Alitretinoin has been approved for the topical treatment of cutaneous Kaposi's sarcoma as a 0.1% concentration gel, three times a day. Systemic use is still under evaluation for this disease and has been recently approved for the treatment of chronic eczema of the hands and/or feet.

Take-Home Messages

- Retinoids are natural or synthetic compounds with vitamin A similar activity. They have the ability to activate nuclear retinoid receptors and are classified in generations.
- They represent a class of medications widely used in dermatological practice. Understanding their actions, indications and side effects allow their use with security and good/excellent results.

- Topically, their main indications are for acne and photoaging, and it can be a good option for psoriasis.
- Oral isotretinoin is the gold standard treatment for acne vulgaris, with some other good indications as keratinization diseases like Darier, ichthyosis, dissecans scalp folliculitis, and gram-negative folliculitis.
- Acitretin is a classical treatment for moderate-to-severe psoriasis vulgaris and is even more effective in pustular and erythrodermic psoriasis. It is also the preferred option for the treatment of keratinization disorders.
- Teratogenicity is a major concern about systemic retinoids. They are absolutely contraindicated in pregnancy (FDA category X) and lactation.
- Retinoid dermatitis is the main side effect of retinoic acid. When applied topically for acne treatment, it cannot be considered as worsening or the clinical results or as allergy.
- Many adverse effects are related to systemic retinoids and are essentially dose dependent with the exception of teratogenicity. With regular consultations and laboratory tests, they can be easily managed.

Cross-References

- ▶ Approach in Photodamaged Skin, Melasma, Acne, and Rosacea
- ▶ Chemical and Physical Sunscreens
- ▶ Evaluation and Classification of Aging
- ▶ Oral Photoprotection
- ▶ Photoprotection: Concept, Classification, and Mechanism of Action
- ▶ Skin Anatomy, Histology, and Physiology

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Hydroxy Acids

Ediléia Bagatin and Lilia Ramos dos Santos Guadanhim

Abstract

Hydroxy acids (HAs) represent useful substances for skin care and chemical peelings and have been used typically in concentrations ranging from 2% to 70%, depending on the indication, pH, formulation, and application schedule. The higher the concentration and the lower the pH of the product, the greater the exfoliative, epidermolytic, and even toxic and corrosive action.

The most widely used hydroxy acids are glycolic, mandelic, and salicylic acids. Recently, other substances like β-lipohydroxy acids (BLHAs) and gluconolactone have been developed in order to enhance efficacy and diminish irritation.

The main effects of hydroxy acids in the skin are hydration, exfoliation, acceleration of collagen synthesis and modulation of matrix degradation, epidermal turnover regulation, inhibition of tyrosinase activity, and free radical neutralization.

The uses of hydroxy acids include the treatment of dry skin, hyperkeratinization, acne, rosacea and sensitive skin, hyperpigmentation, wrinkles, and photoaging, with a high tolerance and good safety profile.

Keywords

Hydroxy acids • α-Hydroxy acids • AHA • Salicylic acid • Glycolic acid • Bionic acid • Polyhydroxy acid • β-Hydroxy acids • β-Lipohydroxy acid • Chemical peels • Mandelic acid • Gluconolactone • Photoaging • Hyperpigmentation • Acne

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Introduction

In the mid-1970s, Van Scott and Yu found that hydroxy acids (HAs) with a hydroxyl group at the α- or β-position, when applied topically, had a very specific effect on hyperkeratinization. This effect was clinically expressed by an initial abrupt detachment of the hyperkeratotic stratum corneum at its innermost level, stratum compactum, distal to the stratum granulosum, providing beneficial effects for ichthyosis, dry skin, keratoses and warts, and follicular hyperkeratosis, including that occurring in acne (Van Scott and Yu 1974, 1984).

Since then, HAs transformed skin care and have been used typically in concentrations ranging from 2% to 70%. In low concentrations (4–10%), the HAs are ubiquitous components of nonprescription creams and lotions that are promoted as being effective for ameliorating skin aging. In high concentrations (>20%), these preparations are used as chemical "peels" to treat calluses, keratoses, acne, psoriasis, and photoaging (Kornhauser et al. 2010).

Sustained applications of α-HAs (AHAs) and β-HAs (BHAs) result in plumping of the skin, and, although some epidermal thickening occurs, dermal thickening is correlated with biosynthesis of glycosaminoglycans (GAGs), collagen, and improved quality of elastic fibers. These dermal changes improve fine lines and wrinkles (Ditre et al. 1996).

α-Hydroxy Acids (AHAs)

The AHAs are organic carboxylic acids with one hydroxyl group attached to the α-position of the carboxyl group. The hydroxyl group in the AHA is neutral, and only the carboxyl group provides an acidic property. Many AHAs are present in foods and fruits and, therefore, are called fruit acids. Naturally, it occurs in grapes, sugarcane juice, and sugar beets. It is strongly hygroscopic, so it has to be kept in closed bottles.

Glycolic acid (hydroxyacetic acid) is the smallest and simplest representative of AHA and also the most widely used in skin care.

Lactic acid, with optimal biologic activity in its L-form, is the next smallest molecule and is also used in various topical formulations to exfoliate the skin and also to provide antiaging properties (Kornhauser et al. 2010). It ameliorates the skin by increasing the levels of stratum corneum ceramides and glycosaminoglycans (Piérard et al. 1999).

Some AHAs contain a phenyl group as a side-chain substituent. This changes the solubility profile of AHA, providing increase lipophilicity over conventional water-soluble AHAs, and can be used to target oily and acne-prone skin. Examples include mandelic acid (phenyl glycolic acid) and benzilic acid (diphenyl glycolic acid) (Green et al. 2009). The addition of mandelic acid and benzilic acid to 0.5% salicylic acid has been shown to provide significant oil-reducing properties and a favorable tolerability profile while offering a concentration of salicylic acid that can be used nearly worldwide (Green 2005).

In 1998, the Cosmetic Ingredient Review (CIR) Expert Panel recommended limitations on the concentration of AHAs (<10%) and the pH (at or above 3.5) of cosmetic products containing AHAs. In addition, these products should be formulated to avoid sun sensitivity, and consumers should be advised to use daily sun protection (Kornhauser et al. 2010).

The chemical structure, acidity, and source of the different AHAs are presented in Table 1.

Mechanism of Action

An important epidermal effect is the increase of water holding capacity due to AHA application along with an increase of skin hydration and skin turgor. Besides, AHAs induce desquamation, plasticization, and normalization of epidermal differentiation by interfering with intercellular ionic bonding, thereby reducing corneocyte cohesion and thus inducing keratolysis. The higher the concentration of the acid and the lower the pH of the product, the faster keratolysis is induced and may even lead to epidermolysis (Babilas et al. 2012).

Table 1 AHAs – chemical structure, acidity, and source (Babilas et al. 2012)

Name	Molecular formation	Acidity (pKa)	Natural source
Lactic acid	$C_2H_6O_3$	3.86	Fermented milk products
Citric acid	$C_6H_8O_7$	3.09	Citrus fruits
Mandelic acid	$C_8H_8O_3$	3.41	Bitter almonds
Glycolic acid	$C_2H_4O_3$	3.83	Sugarcane
Tartaric acid	$C_4H_6O_6$	3.22	Fermented grapes
Ascorbic acid	$C_6H_8O_6$	4.10	Fruits
Malic acid	$C_4H_6O_5$	3.40	Apples

Evidence has been published on the AHA's ability to increase dermal and epidermal glycosaminoglycans (GAGs) (Ditre et al. 1996; Bernstein et al. 1997) and to prevent both epidermal and dermal atrophy resulting from long-term topical corticosteroid use (Lavker et al. 1992).

In vitro studies using cultured human skin fibroblasts have shown a dose-dependent increase of cell proliferation and collagen production (Kim and Won 1998).

Other effects documented in literature are increased synthesis of GAG, increased dermal thickness, fibroblast proliferation, and induction of factor XIIIa transglutaminase (Grossman and Matarasso 2002).

Okano et al. conducted a study that investigated the effects of glycolic acid on the dermal matrix metabolism of keratinocytes and fibroblasts using in vitro and ex vivo (human skin biopsies) systems. That study showed that glycolic acid not only directly accelerates collagen synthesis by fibroblasts but also modulates matrix degradation and collagen synthesis through keratinocyte-released cytokines. Their experiments confirmed that IL-1a is one of the primary mediators regulating matrix degradation that are released from keratinocytes after glycolic acid treatment. On the basis of their findings, the authors suggest that glycolic acid contributes to the recovery of photodamaged skin through various pathways, depending on the skin cell type (Okano et al. 2003).

Safety Profile

Usually, a daily-based application by patients themselves using a concentration up to 20% is tolerated very well and evokes only a minor rate of side effects. The potential side effects are mild-to-moderate skin irritation, stinging or burning sensation, pain, and erythema.

If a higher concentration is used, i.e., office-based treatments, the side effects become more frequent. The possible adverse events include pain, blistering, purple or crusting, erythema, hypopigmentation, hyperpigmentation, atrophy, ulceration, scarring, hypertrophic scarring or keloid formation, and infection.

The most frequent side effect following AHA's peeling is a persistent erythema. While burning sensation probably lasts only for hours in case of a mild peeling, it may last for months if a deep peeling is applied (Babilas et al. 2012).

B-Hydroxy Acids (BHAs)

The BHAs are organic carboxylic acids having one hydroxyl group attached to the β-position of the carboxyl group. The hydroxyl group in the BHA is neutral in nature, and the carboxyl group provides the acidic property (Green et al. 2009).

Malic acid and citric acid are prominent representatives in this category.

Citric acid is widely used in topical formulations as an antioxidant and pH adjustor, and its antiaging benefits are well established (Bernstein et al. 1997).

Salicylic Acid (SA)

In cosmetic and dermatologic literature, salicylic acid (SA) is often described as a BHA, but that classification is incorrect (Yu and Van Scott

1997.) In SA, both hydroxyl and carboxyl groups are directly attached to an aromatic benzene ring, and both exhibit acidic properties. In contrast, the hydroxyl groups in AHAs, BHAs, and PHAs are neutral under the conditions used in clinical and cosmetic settings. On the basis of knowledge to date, SA does not function physiologically or therapeutically as a BHA. Furthermore, AHAs are soluble in water and SA is not.

SA is widely used in cosmetic formulations (concentrations 2–4%) and also therapeutically as a keratolytic agent to treat skin conditions such as calluses, keratosis, acne, and photoaging. It is especially useful in subjects with oily skin (Kornhauser et al. 2010.)

Several experimental and clinical studies have found that topically applied SA is photoprotective, having a pronounced filter effect when applied prior to UVB exposure (Kornhauser et al. 2010).

The antibacterial action of SA has been known for many decades. A study indicates that SA acts at the level of transcription to downregulate the production of fibrinogen, fibronectin, and α-hemolysin virulence factors necessary for bacterial replication in host tissues (Herrmannn 2003).

SA at high concentrations (30%) induces hyperplasia of the epidermis and improves the dispersion of melanosomes, which makes it useful in treating hyperpigmentation (Klingman and Klingman 1998).

It is important to remember that toxicity and hepatic injury are possible side effects of SA. It should be applied only to small surface areas and for limited periods of time.

β-Lipohydroxy Acid (BLHA)

A C-8 derivative of SA known as β-lipohydroxy acid (BLHA), developed in the late 1980s, has been proposed as an exfoliant and as a treatment for photoaged skin and acne. BLHA has an eight-carbon fatty chain linked to the benzene ring making it more lipophilic than SA.

BLHA was shown to have a good safety profile with lower irritation when compared to glycolic acid (GA). It has antibacterial effects, which are ideal for the treatment of acne (Kornhauser et al. 2010). It also has a marked affinity for the comedos. After a 1-month treatment with 2% BLHA, there was a decrease of the number of follicular casts compared to placebo ($p < 0.01$) (Piérard et al. 1999).

Creams containing 2% SA or BLHA were found to enhance the shedding of corneocytes and reduce the thickness of the stratum corneum. The penetration of SA and the AHAs is relatively rapid, and consequently the breakdown of central corneosomes occurs throughout the stratum corneum. BLHA, on the other hand, appears to have a more restricted action due probably to its lipophilic nature and its relatively slower penetration. This molecule causes the desmosome to fracture at the stratum disjunctum/compactum interface, where it produces relatively clean breaks and therefore more closely mimics the physiologic process.

In clinical trials using 1% BLHA, volunteers reported significant improvement in softness, tonicity, and comfort of the skin (Saint-Léger et al. 2007). In isolated human skin, 1.5% BLHA has been found to significantly increase cell renewal versus control versus 5% SA. An order of potency for this response has been established: 0.05% all-trans-retinoic acid >2% BLHA >> 10% GA (Piérard et al. 1999).

BLHA (1–5%) dose-dependently stimulated collagen formation in a human reconstructed skin model and increased filaggrin content in human skin biopsies (Piérard et al. 1999).

When applied 3x/day, a low concentration (0.3%) of BLHA was found to slightly but significantly reduce skin pigmentation induced by daily exposure to sub-erythemal UV dose. This protective effect can be explained by its antioxidant properties (Piérard et al. 1999).

Table 2 presents a comparison of the effects of retinoic, glycolic, and β-lipohydroxy acids.

Polyhydroxy Acids (PHAs)

A new generation of AHAs, called polyhydroxy acids (PHAs), provides similar effects, but with less irritation response. The PHAs are organic carboxylic acids with two or more hydroxyl groups in the molecule attached to carbon atoms

Table 2 Comparison of retinoic, glycolic, and β-lipohydroxy acids (Piérard et al. 1999)

	Retinoic acid	Glycolic acid	BLHA
Pigmentation – epidermal pigmentation	↓	↓	↓
Pigmentation – melanosome cluster frequency	↓	-	↓
Exfoliation – shedding of corneocytes	↑↑	↑	↑↑
Exfoliation – thickness of the stratum corneum	↓	↓	↓
Exfoliation – smoothness of the skin	↓	↓	↓
Acne – comedolytic activity	Yes	No	Yes
Acne – antibacterial activity	No	-	Yes

of an aliphatic of alicyclic chain. All the hydroxyl groups in the PHA are neutral, and only the carboxyl group provides its acidity (Green et al. 2009).

Gluconolactone is the most commercialized PHA in skin care products, because it is readily available and delivers the antiaging benefits of HAs, in addition to strengthening skin barrier function and being a gentle, moisturizing, antioxidant/chelating substance.

An in vitro cutaneous model of photoaging demonstrated that gluconolactone protects – up to 50% – against ultraviolet (UV) radiation. As the UV absorption of gluconolactone is low, these findings were attributed to the ability of gluconolactone to chelate oxidation-promoting metals and trap free radicals (Bernstein et al. 2004). Gluconolactone can be formulated with oxidative drugs, such as benzoyl peroxide, to help reduce irritation potential and erythema cause by the oxidative drug (Kakita and Green 2006).

Gluconolactone has demonstrated efficacy for improving skin moisturization, fine lines and wrinkles, skin laxity, uneven skin tone, roughness, and pore size (Green et al. 2001).

Bionic Acids (BAs)

The BAs are chemically classified as aldobionic acids. They consist of one carbohydrate monomer chemically linked to analdonic acid and lactobionic acid; maltobionic acid and cellobionic acid are some examples.

Because of the multiple hydroxyl groups, lactobionic acid is a strong humectant and more effective than regular AHAs, and it could be presumed that it increases the synthesis of GAGs in the skin, due to the presence of D-galactose, a naturally occurring sugar needed for the GAG synthesis and skin metabolite, attached to the polyhydroxy acid structure (Tasic-Kostov et al. 2010).

Although the BAs are larger molecules than the traditional AHAs, they are small enough to penetrate the skin at approximately 358 Da, and their pKa is roughly equivalent to smaller AHA molecules.

BAs are hygroscopic materials that readily attract and retain water, forming a gel matrix when their aqueous solution is evaporated at room temperature. Formation of a gel matrix may add protective and soothing effects for inflamed skin. Indeed, formulations containing BA are well tolerated and help calm the skin when applied after cosmetic procedures that weaken the skin's barrier, including superficial HA peels and microdermabrasion (Green et al. 2009).

Green performed a study of the effects of lactobionic acid-containing products and revealed improvement in all photoaging and texture parameters on exposed skin, with no signs of intolerance (Green 2000).

Lactobionic acid also functions as an inhibitor of the matrix metalloproteinase (MMP) enzymes. The excessive activity of MMPs occurs with age and sun exposure, contributing to wrinkle formation, skin laxity, and visible telangiectasia. The use of BAs to inhibit MMPs may provide a significant benefit in the prevention of photodamage (Green et al. 2009).

Tasic-Kostov et al. conducted a study to assess the safety and efficacy of lactobionic acid as compared to glycolic acid and found out that lactobionic acid resulted in improved skin benefits as compared with corresponding glycolic acid

Table 3 Safety and mechanism of action of hydroxy acids (Kornhauser et al. 2010)

Types of HAs	Safety evaluation	Mechanism of biological action
AHA	Not mutagenic or carcinogenic, not reproductive or developmental toxins, not skin sensitizers	Reduced Ca ion concentration in the epidermis disrupts cellular adhesions by removing Ca ions from the cell adhesions by chelation allowing for exfoliation, promoting cell growth, and retarding cell differentiation
Glycolic acid	Increased solar-stimulated radiation sensitivity in the human skin Increased epidermal and dermal levels of hyaluronic acid and collagen gene expression	Acceleration of collagen synthesis by fibroblasts and also modulation of matrix degradation and collagen synthesis through keratinocyte-released cytokines Accelerated epidermal turnover and inhibition of melanin formation in melanocytes by directly inhibiting tyrosinase activity
PHA	Photoprotective	Function as a chelating agent and exhibits potency in scavenging free radicals
SA	Enhances percutaneous penetration, not photosensitizer, not phototoxic	Acts at the level of transcription to downregulate the production of fibrinogen, fibronectin, and α-hemolysin virulence factors necessary for bacterial replication in host tissues

formulations, particularly with respect to skin irritation and barrier impairment.

The efficacy of both lactobionic and glycolic acid was higher when used in vehicles based on analkylpolyglucoside (APG) emulsifier, emphasizing the importance of vehicle on the effects of topical actives (Tasic-Kostov et al. 2010).

The safety profile and mechanism of action of the HAs are shown in Table . 3.

Clinical Uses of HAs

The indication for treatment with the HAs depends mainly on concentration, pH, formulation, and application time.

The higher the concentration and the lower the pH of the product, the greater the exfoliative, toxic, and corrosive action. Lower concentrations with 5–20% of HAs are formulated in creams or gels for use prior to peeling and for long-term application (Babilas et al. 2012).

Dry Skin and Hyperkeratinization

A large group of AHAs, when applied topically to patients with any form of hyperkeratosis, diminish the thickness of the stratum corneum by diminishing corneocyte cohesion, which is first seen at the lower, newly forming levels of the stratum corneum (Van Scott and Yu 1984).

Topical use of AHA formulations on xerotic skin restores the stratum corneum and epidermis to a more normal clinical and histologic state. Combination HA formulations that contain PHAs and BAs are found to have unparalleled efficacy for treating xerosis and for treating otherwise treatment-resistant conditions such as calluses and fissured plantar and palmar skin (Green et al. 2009).

For example, the use of a cream containing 5% lactic acid, 5% glycolic acid, 5% mandelic acid, and a 5% blend of gluconolactone and maltobionic acid (pH 3.7) once daily for 3 weeks improved hyperkeratotic heels. Moreover, lamellar ichthyosis may be treated successfully with the same combination, twice a day for 2 weeks (Green et al. 2009).

For usual severe cases of lamellar ichthyosis or X-linked ichthyosis, optimum effectiveness is achieved with unneutralized formulations as follows: glycolic acid, mandelic acid, saccharic acid, tartaric acid, malic acid at 5–10%, and gluconolactone at 10–20%. Lactic acid formulations partially neutralized with ammonium hydroxide have provided equivalent effectiveness

in 8–12% formulations. The preparations should be applied thinly 2–4 times daily for 1 to 3 weeks until the clinical appearance of the skin approaches normal (Van Scott and Yu 1984).

Sensitive Skin and Rosacea

One of the distinguishing benefits of the PHAs and BAs is their gentleness on the skin. Compared with glycolic acid and lactic acid, PHAs and BAs do not sting or burn. Previous studies have demonstrated compatibility with sensitive skin, even on rosacea and atopic dermatitis (Rizer et al. 2001a, b).

Moreover, partly because of their gentleness, concurrent use of products with gluconolactone and a topical drug containing azelaic acid has been shown to improve therapeutic outcomes for rosacea by reducing skin redness and diminishing the appearance of telangiectasia. The latter effect may occur as a result of the ability of gluconolactone to increase skin thickness. Patient tolerability of medication containing azelaic acid also improved (Draelos et al. 2006).

Hyperpigmentation

AHAs, such as glycolic acid and lactic acid, have been reported to be effective in treating pigmentary lesions including melasma, solar lentigines, and post-inflammatory hyperpigmentation. The proposed mechanism of this effect is epidermal remodeling and accelerated desquamation, which should result in quicker pigment dispersion (Kornhauser et al. 2010).

In 2003, Usuki et al. published an in vitro study that showed that glycolic acid and lactic acid (300–500 μg/mL) suppressed melanin formation by directly inhibiting tyrosinase activity in human and mouse melanoma cells. Both the transcription and translation of tyrosinase were decreased significantly, with reduced enzyme function. The authors concluded that glycolic acid and lactic acid might work not only by accelerating epidermal turnover but also by directly inhibiting melanin formation in melanocytes (Usuki et al. 2003).

Clinical studies showed that forearms treated with 25% lactic acid lotion, two times a day for 6 months, had fewer lentigines and less mottled hyperpigmentation and were more plumped (Green et al. 2009).

The use of PHAs also leads to significant skin lightening, although the mechanism by which that occurs has not yet been elucidated (Grimes et al. 2004).

Wrinkles and Photoaging

Ultraviolet (UV) exposure induces a wide range of damaging chemical reactions in the skin. Chronically exposed skin becomes photoaged, a condition characterized by a thicker dermis (degradation of the elastic fiber network with accumulation of breakdown products and deposition of lysozyme) and thinner epidermis with cellular atypia and loss of polarity, irregular pigmentation, wrinkling, and coarseness. Although the gold standard for treatment is tretinoin, the efficacy of hydroxy acids has been repeatedly reported (Piérard et al. 1999).

The antiaging benefits of AHAs have been known for many years. In ancient times, Cleopatra was said to bathe in sour milk, which contains lactic acid, in order to give her skin a youthful appearance (Tran et al. 2015).

The exact mechanism of action for topical AHAs is still unknown; however, the most widely accepted theory is that AHAs remove calcium ions from epidermal cell adhesions by chelation. This results in weakening of the intercellular adhesions, which has an exfoliating effect by causing shedding and flaking of dead and dry cells. The reduced calcium levels also promote further cell growth while slowing cell differentiation, thereby lessening the appearance of wrinkles and making the skin look younger (Tran et al. 2015).

AHAs may also promote increased gene expression of collagen and hyaluronic acid in the dermis and epidermis, which in turn improves plumpness and hydration of the skin (Bernstein et al. 2001).

Previous studies have found substantial increases in dermal thickness that were correlated

with increased amount of hyaluronic acid and other GAGs as well as with qualitative improvements in collagen fibers and improved histologic quality of elastic fibers. The papillary dermis also increased in thickness, with increase prominence of dermal papillae. The effects lasted for months (Ditre et al. 1996).

Glycolic acid also increases the production of collagen, hyaluronic acid, and fibroblast proliferation. Sun-damaged forearm skin was treated with 20% glycolic acid lotion or a lotion vehicle control (oil in water, pH 3.9), twice a day for 3 months. The authors found that this protocol increased epidermal thickness, epidermal and dermal levels of hyaluronic acid, and collagen gene expression. Even small increases in the content of cutaneous hyaluronic acid may result in large changes in epidermal and dermal hydration, affecting skin appearance, texture, and function (Bernstein et al. 2001).

Although GAGs make up only about 0.1–0.3% of the dry weight of the normal dermis, they can bind up to 1000 times their weight in water. Thus, relatively small alterations in the amount of dermal GAGs may result in large changes in epidermal and dermal hydration, affecting skin appearance, texture, and functional ability. GAGs provide an aqueous environment for cell migration, the diffusion of nutrients, and elimination of toxic metabolites. The early provisional matrix in a healing wound consists of fibrin and hyaluronic acid, creating a scaffold for the migrations of cells to the wound site. This allows for the creation of a more permanent, stable matrix composed largely of collagen. Thus GAG deposition is an early event in skin formation preceding the formation of collagen (Bernstein et al. 2001).

Epidermal GAG staining increased 2–2.5 fold after AHA treatment, with nearly identical results for retinoic acid. The dermal effects are also similar to tretinoin. Moreover, glycolic acid-treated skin showed a 2.8-fold increase in type I collagen mRNA, as compared to vehicle-treated control skin. Accumulation of collagen mRNA could be due to increased transcription or decreased mRNA stability, so future studies are needed to help determine the mechanisms of collagen mRNA accumulation (Bernstein et al. 2001).

Rendl et al. investigated the effects of creams containing lactic acid on the secretion of cytokines by keratinocytes in human reconstructed epidermis. They found that topically applied creams containing lactic acid (1.5%, 3%, or 5%) led to a concentration-dependent increase in apoptotic cells compared to the vehicle control. In addition, they found an increase in the secretion of vascular endothelial growth factor (VEGF) over the vehicle control after treatment with 1.5% or 3% lactic acid. The authors concluded that topical application of lactic acid modulates the secretion of cytokines by keratinocytes and that this regulation might represent a mechanism contributing to their therapeutic effects such as photoaging (Rendl et al. 2001).

Newman et al. investigated the histological and clinical effects of 50% glycolic acid peels on photoaged skin. It consisted of a split-face study of glycolic acid 50% versus vehicle once a week for 4 weeks. They assessed a decrease in rough texture and fine wrinkling, fewer solar keratoses, and a slight lightening of solar lentigines. The histologic analysis revealed a thinning of the stratum corneum, an enhancement of the granular layer, and an epidermal thickening, which shows that 50% glycolic acid peels are capable to improve mild signs of photoaging (Newman et al. 1996).

Ditre et al. conducted a placebo-controlled study with patients with moderate-to-severe photoaging. Patients had to apply an AHA-containing lotion (25% glycolic acid ($n = 5$), 25% lactic acid ($n = 5$), or 25% citric acid ($n = 7$), pH 3.5) twice daily for 6 months. There was a 25% increase in skin thickness; the epidermis showed a significant reversal of basal cell atypia, dispersal of melanin pigmentation, and a return to a normal rete pattern. The elastic fibers tented to be longer, thicker, and less fragmented. Ultrastructurally, the basal layer showed more uniform basal keratinocyte nuclei; less clumping of tonofilaments within the cytoplasm, with more perinuclear localization of tonofilaments; and the formation of microvilli. There were only transient tingling and itch sensation as side effects, but these became less noticeable or disappeared with continuous use. Increased skin thickness appears to be caused by increased synthesis of GAGs and collagen, and possibly elastic fibers (Ditre et al. 1996).

Bernstein et al. demonstrated the effects of citric acid in the epidermis and dermis of sun-damaged skin, but highlighted the main role of sunscreens (Bernstein et al. 1997).

Acne

For the treatment of acne-prone skin or mild acne, predominantly, cosmetic products containing HAs 5–20% are on the market. The pH value usually ranges from 2 to 8. However, the concentration and a pH significantly lower than the physiological pH of the skin are primarily responsible for the comedolytic and antimicrobial effects.

AHAs depending on the concentration used reduce the coherence of the superficial and also follicular corneocytes in the stratum corneum. In addition, because of pH changes, proteases like aspartase and cysteine proteases are likely to be activated in the outer stratum corneum, and, thus, the desquamation process could be enhanced as seen by an increased stratum corneum turnover time. Moreover, it is well known that decreasing the pH on the skin surface regulates and impairs microbial growth, in particular of *Propionium* bacteria.

A 10% glycolic acid containing oil-in-water emulsion improved mild acne applied as a monotherapy for 45 days, when compared to placebo. The application of glycolic acid formulation for 6 weeks led to a significant decrease in the pH from 6.2 to 5.4 in volunteers suffering from acne or acne-prone skin. An acidic pH on the skin surface exerts antibacterial effects, and it can be assumed that it yields a reduction of *P. acnes* in the treated patients. The tolerability of glycolic acid 10% is expected to be better when compared to benzoyl peroxide-containing products or topical retinoids. In addition, glycolic acid is not bleaching or discoloring textile, and antibiotic resistance is unlikely to occur (Abels et al. 2011).

Salicylic acid exhibits keratolytic properties as it solubilizes intracellular cement. Its lipid solubility permits the interaction with multilamellar structures surrounding the keratinocytes in the stratum corneum, thereby exhibiting follicular atrophy and comedolytic action within the sebaceous unit. SA is effective in comedonal and inflammatory acne. It also facilitates the resolution of post-inflammatory hyperpigmentation of the face (Kar et al. 2013).

Kessler et al. compared the efficacy of alpha- (30% glycolic acid) and beta-hydroxy (30% salicylic acid) acids as peel agents, in a split-face, double-blind, randomized controlled study on patients suffering from mild-to-moderate severe facial acne vulgaris. The acids were randomly applied to one side of the face every 2 weeks for a total of six treatments. Both peels reduced papules and pustules after the second treatment ($p < 0.05$) and did not differ in effectiveness. More adverse events were reported with the glycolic acid peel though (Kessler et al. 2008).

Uses as a Peeling Agent

Glycolic acid and lactic acid are AHAs that have been used commonly as peeling agents.

In high concentrations, up to 70% or greater, they can be applied to the skin for short times to achieve substantial desquamation and accelerate the epidermal and dermal renewal for rejuvenation and adjunctive care of acne, rosacea, and hyperpigmentation (Green et al. 2009).

HA peels are good options for pre- and post-treatment for laser resurfacing. A 50% glycolic acid peel 2 and 4 weeks before resurfacing and a 70% glycolic acid peel immediately before laser treatment (neutralize peel and begin resurfacing) may require fewer passes with the laser and result in fewer complications (Petratos 2000).

A study comparing the use of oral isotretinoin alone versus oral isotretinoin with 20% salicylic acid peels once every 2 weeks for 16 weeks concluded that both are effective but the clearance of acne was significantly better with combined therapy with no further adverse effects (Kar et al. 2013).

Synergy with Topical Drugs

HAs can be used to enhance and improve therapeutic effects of certain medicinal agents. For

example, the AHA lactic acid and its ammonium salt prevent dermal atrophy associated with the topical use of corticosteroids (Lavker et al. 1992). This is presumably due to AHA stimulation of collagen and GAGs synthesis.

It is possible that HAs may increase the affinity of the receptor molecule toward the topical agent, acting as a better and more efficient coenzyme or as an activator by disrupting barriers and removing inhibitors for better binding of the agent toward its receptor molecule. Such may be the case when AHAs are combined with topical corticosteroids in the treatment of psoriasis – the enhanced therapeutic effects are not due to increased penetration and can be achieved by the use of a combination formulation or by an alternative use of separate formulations (such as different morning/evening preparations). For example, there is better clinical response in the use of 0.5% benzilic acid added to clobetasol propionate 0.05% in the treatment of psoriasis than clobetasol propionate 0.05% alone (Green et al. 2009).

Conclusion

HAs is a class of substances which can be used as topical products or peeling agents. They represent good option for the treatment of hyperkeratinization, photoaging, hyperpigmention, and acne, with a high tolerance and good safety profile.

Take-Home Messages

- Hydroxy acids are safe and well tolerated even in a sensitive skin in proper formulations.
- The most important indications are acne, hyperpigmentation, and photoaging.
- Office-based treatments should be performed by trained dermatologists in order to avoid complications such as epidermolysis, blistering, scarring, persistent erythema, and post-inflammatory hyperpigmentation.

Cross-References

- ▶ Approach in Photodamaged Skin, Melasma, Acne, and Rosacea
- ▶ Chemical and Physical Sunscreens
- ▶ Evaluation and Classification of Aging
- ▶ Oral Photoprotection
- ▶ Photoprotection: Concept, Classification, and Mechanism of Action
- ▶ Skin Anatomy, Histology, and Physiology

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Vitamins and Other Antioxidants

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Abstract

The term cosmeceutical was created over 25 years ago to define products with active substances that cannot be considered cosmetics or drugs. Oxidative stress has been recognized as a fundamental factor in the process of skin aging, since the skin is constantly exposed to solar radiation and environmental pollution, which are capable of inducing the formation of free radicals and reactive oxygen species. Topically applied antioxidants are an important group of cosmeceutical agents capable of preventing and reducing UV-induced skin damage, by protecting skin cells against the action of free radicals. A variety of antioxidants can be applied topically, including vitamins and its derivates, enzymes, minerals, and plant-derived compounds. Vitamins are essential compounds for many functions of the human organism. Scientific evidence shows that, in addition to their specific functions, certain vitamins are useful for prevention, as well as for topical treatment of photoaging and chronologic skin aging. Cosmeceuticals that contain topically applied vitamins have an increasing role in skin care. The mechanisms of action of these molecules, the proper formulation for topical use, and the scientific data that support their efficacy are important aspects to consider when prescribing antioxidant cosmeceuticals.

Keywords

Vitamins • Antioxidants • Oxidative stress • Vitamin C • Vitamin E

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Contents

Introduction

The desire to maintain a healthy and youthful look has created a growing demand for antiaging skin care products. Research focusing on the processes that lead to skin damage, both intrinsically and extrinsically, led to the development of substances that are able to prevent the damage and counteract the deleterious effects that contribute to skin aging (Manela-Azulay and Bagatin 2009).

The skin is constantly exposed to solar radiation and environmental pollution, which are capable of inducing the formation of free radicals and reactive oxygen species (ROS) (Polsjak and Dahmane 2012). Free radicals are defined as molecules or fragments of molecules containing one or more unpaired electrons in their external orbitals (Andreassi and Andreassi 2003).

Under physiological conditions, human skin possesses different antioxidant mechanisms and repair systems that prevent cellular damage from severe oxidative stress. However, the levels of these antioxidants are reduced by age and exposure to environmental stress, such as ultraviolet (UV) radiation, tobacco smoke, alcohol consumption, and pollution. With the depletion of such mechanisms, oxidative stress can lead to harmful effects in skin's function and structure. ROS-induced oxidative stress has been linked to cancer, inflammation, aging, and photodamage (Oresajo et al. 2012).

Topically applied antioxidants are an important group of cosmeceutical agents capable of preventing and reducing UV-induced skin damage, by protecting skin cells against the action of ROS (Oresajo et al. 2012). A variety of antioxidants can be applied topically, including vitamins and its derivates, enzymes, minerals, and plant-derived compounds.

Antioxidants may be combined with other cosmeceuticals and skin actives, resulting in complementary mechanisms of action to prevent skin aging. For example, the addition of botanical antioxidants and vitamins C and E to a broad-spectrum sunscreen may improve UV protection, by acting through different, complementary mechanisms (Matsui et al. 2009).

Vitamins are essential for normal metabolism, and while some can be synthesized, others need to be obtained by an adequate diet. There is some evidence showing that, in addition to their specific function, certain vitamins are useful for prevention and treatment of photoaging (Manela-Azulay and Bagatin 2009).

The cosmetics market has seen an increase in the number of skin care products that claim to have antioxidant activity (Andreassi and Andreassi 2003). Cosmetics labeled with the word "antioxidant" are popular and favored by the consumer seeking to treat or prevent signs of photoaging. However, there is little clinical evidence to support the efficacy of many of those products. Most scientific evidence shows that some of those ingredients have possible in vitro

activity, but few have been submitted to clinical trials to confirm the activity and efficacy in the human skin in vivo.

The mechanisms of action of these molecules, the proper formulation for topical use, and the scientific data that support their efficacy are important aspects to consider when prescribing antioxidant cosmeceuticals, in order to achieve an adequate routine of skin care and ultimately prevent the signs of photoaging and improve skin appearance (Chen and Weng 2012).

Oxidative Stress and Skin Aging

The human skin is particularly exposed to oxidative stress. Not only it is supplied with oxygen from the blood; it is also in direct contact with the external environment, where different factors, such as UV exposure, ozone, and chemical pollutants, might induce the formation of free radicals and ROS (Andreassi and Andreassi 2003).

ROS are produced during the physiological processes of cellular metabolism, when excess electrons generated in the mitochondrial respiratory chain are donated to molecular oxygen to generate superoxide anions (Oresajo et al. 2012). ROS are actually required, in a certain concentration, for normal cell function; Poljsak et al. (2013b), for example, the immune cells with phagocytic activity generate free radicals in order to combat pathogens. However, this endogenous formation of free radicals also contributes to the process of chronological aging that every cell goes through, by mechanisms such as DNA damage, oxidation of membrane lipids and proteins, inflammation and telomere shortening (Rahman 2007).

Skin cells are submitted to additional oxidative stress, generated mainly by UV irradiation, accelerating the intrinsic aging process. According to Pattison and Davies, UV radiation can harm the cell structure and function via two different mechanisms: (a) direct absorption of light by cellular components that lead to excited state formation and chemical reactions and (b) absorption by endogenous or exogenous sensitizers (photosensitizers), such as porphyrins and flavins, that are excited to their triplet state (Pattison and Davies 2006). UVR can induce oxidative damage to both nuclear and mitochondrial DNA, who also plays an important role in the aging mechanisms. Therefore, photoaging represents the superposition of the biologic effects of sun irradiation and the naturally occurring intrinsic aging.

Free radicals of biological importance include hydroxyl, superoxide, nitric oxide, ethyl, and peroxyl. Peroxynitrite superoxide, hypochlorous acid, hydrogen peroxide, singlet oxygen, and ozone are not free radicals but can lead to free radical reactions in living organisms (Poljsak and Dahmane 2012). The term reactive oxygen species (ROS) is often used to include not only free radicals based on oxygen but also some non-radical by-products of oxygen, such as hydrogen peroxide and singlet oxygen (Andreassi and Andreassi 2003).

Several factors can aggravate extrinsic skin aging, such as ionizing radiation, alcohol intake, poor nutrition, tobacco smoke, and environmental pollution. However, the main source of free radical formation in the skin is exposure to UV radiation. Since the ozone layer in the atmosphere absorbs all UVC and most UVB, 95% of the radiation that reaches the surface of the planet is UVA, and just 5% is UVB. UVB penetrates only into the epidermis and is the major cause of sunburns. UVA penetrates more deeply, acting mainly in the dermis of the skin.

DNA damage due to ROS is not a rare event. It is estimated that human cells sustain an average of 10^5 oxidative hits per day, due to the generation of free radicals by cellular oxidative metabolism (Fraga et al. 1991). Cellular antioxidant mechanisms are therefore crucial to prevent structural damage and mutations. They are constituted of enzymes, such as catalase, peroxidase, superoxide dismutase, glutathione (GSH) peroxidase, and glutathione reductase, and nonenzymatic low-molecular-weight molecules, such as ascorbic acid, uric acid, ubiquinol, and tocopherol. They prevent oxidation of biological molecules, reducing the formation of free radicals or quenching the already formed ROS

(Pandel et al. 2013). In the cytoplasm, GSH and vitamin C are the most important antioxidants, while in the cell membrane, α-tocopherol is the most abundant agent. The upper layers of the epidermis, such as the stratum corneum, have higher concentration of these antioxidants, compared to the dermis (Poljsak et al. 2013a). Some of those enzyme systems use metals, like copper, zinc, manganese, and selenium, as cofactors.

UV exposure can compromise antioxidant defenses, decreasing the levels of catalase, superoxide dismutase, GSH peroxidase, and antioxidants vitamins (Rhie et al. 2001). Long-term exposure to free radicals can deplete the body's own endogenous antioxidants. Overtime, the consequences of the increasing oxidative stress are DNA damage and mutations, reduction in protein functions, and peroxidation of membrane lipids.

There is activation and upregulation of matrix metalloproteinase (MMP) genes, such as MMP 1, 3, and 9, enzymes that degrade collagen. There is also downregulation of collagen I and III genes.

Free radicals induce peroxidation of polyunsaturated fatty acids of the horny layer, leading to skin xerosis. They also induce depolymerization of polysaccharides, such as hyaluronic acid, altering the biomechanical properties of the skin (Andreassi and Andreassi 2003).

Cross-linking of skin proteins, due to the oxidation of some amino acids, such as collagen and elastin, results in stiffening, wrinkling, and aging of the skin (Oresajo et al. 2012).

All these events are mediated by the formation of ROS, making them a fundamental factor in the process of skin aging (Kohen and Gati 2000).

Topical Antioxidants

For effective topical use as a cosmeceutical, an antioxidant must have certain properties: (1) it must be able to penetrate and reach high concentrations specially on the upper layers of the skin; (2) it must be able to protect cells from oxidative stress; (3) there must be no local or systemic toxicity; (4) it must be suitable for incorporation in skin care products; and (5) it must be stable after included in the final product and applied to the skin (Andreassi and Andreassi 2003).

Antioxidants are notoriously unstable and may become easily oxidized and inactive. Ensuring they stabilize in formulation, penetrate properly in the epidermis, and maintain their biological activity is the main challenge in formulating a topically applied antioxidant.

Care must be taken to protect the antioxidants from neutralizing each other. Generally, antioxidants are more stable in acidic pH. It has been shown that the addition of ferulic acid, a phenolic antioxidant found in plants, enhanced stability of a solution of L-ascorbic (vitamin C) and α-tocopherol (vitamin E) (Lin et al. 2005).

In order to increase penetration of the active principle, several strategies may be used, such as the use of penetration enhancers (surfactants, emollients, and solvents), the use of liposomes (small-sized lipid bilayer structures that encapsulate the antioxidants, protecting them from oxidation), and the use of nanocapsules (lipophilic core surrounded by a polymeric material) (Oresajo et al. 2012).

Higher dosages of a compound do not necessarily increase the efficacy of an antioxidant formulation, since the skin absorption of that compound may reach a limit.

Novel antioxidants that are more stable, bioavailable, and skin penetrable are constantly being developed, resulting in products that are more capable of reaching the targets in the skin and promoting its antiaging effect (Table 1).

Cosmeceutical with Vitamins and Other Antioxidants

Vitamin C

Vitamin C, or L-ascorbic acid, is the most abundant antioxidant in the human skin. Most animals and plants are able to synthesize vitamin C, but humans and other primates lost the capacity to produce L-gulonolactone oxidase, the enzyme

Table 1 Vitamins and antioxidants: classification, mechanism of action, indications, and advantages and disadvantages

Vitamins and other antioxidants	Classification	Mechanism of action/function	Indications	Advantages and Disadvantages
Vitamin C	Water-soluble vitamin	Cofactor for collagen synthesis; anti-inflammatory; support other antioxidants; lightening effect	Photodamaged skin; aging; melanoses	Useful agent for intrinsic and extrinsic aging
Vitamin E	Fat soluble vitamin	Photoprotection; anti-inflammatory; moisturizing	Photodamaged skin	Synergistic effect with vitamin C Few studies about topical vitamin E
Vitamin K	Liposoluble vitamin	Chemotaxis; phagocytosis; anti-inflammatory; blood coagulation	Bruising; vascular manifestations	Skin irritation is common with topical vitamin K
Vitamin B3 (nicotinamide)	Water-soluble vitamin	Anti-inflammatory; anti-acne; lightening effect	Photodamaged skin; acne; rosacea; sensitive skin	Non irritating Useful for many dermatoses and sensitive skin
Vitamin B5 (panthenol)	Water-soluble vitamin	Moisturizing; anti-inflammatory	Dry skin, wound healing, sensitive skin	Useful for sensitive skin
Vitamin A (tretinoin)	Liposoluble vitamin	Collagen synthesis; reduce collagen breakage	Intrinsic and extrinsic aging; striae distensae	Efficacy has sufficient evidence base Considered one of the most important agent for aging treatment
Ubiquinone coenzyme Q10	Lipophilic antioxidant	Helps to prevent UVA-induced damage	Fine wrinkles	Few studies
Idebenone	Synthetic analog of coenzyme Q 10	Moisturizing; improves texture	Fine wrinkles	Few studies
Green tea extract	Members of flavonoid family	Radical scavengers; inhibit DNA damage; photoprotection	Extrinsic aging	Few studies
Soy (genistein)	Soybeans	Source of flavonoids; antioxidant; lightening effect; anticarcinogenic; reduce erythema	Aging	Efficacy with few evidence
Lycopene	Carotenoid – plants	photoprotection	Photoaging	Few studies about its topical application
Lutein	Carotenoid – plants	Photoprotection; moisturizing	Photoaging	Efficacy are reported with oral lutein
Pycnogenol (branded name)	Pine tree extract containing bioflavonoids	Photoprotection; antioxidant; anti-inflammatory	Photoaging; pigmentation; melasma	Complementary role with sunscreen
Coffeeberry (branded name)	Antioxidant of coffee fruit	Inhibits collagen breakage	Wrinkles; pigmentation	Few studies
Pomegranate extract	Polyphenolic compounds	Antioxidant; anti-inflammatory; photoprotection	Photoaging	Few studies about antiaging effect in human

(*continued*)

Table 1 (continued)

Vitamins and other antioxidants	Classification	Mechanism of action/function	Indications	Advantages and Disadvantages
Alpha-lipoic acid	Water and fat-soluble natural antioxidant	ROS scavengers	Aging	Contact dermatitis can occur
Resveratrol	Natural antioxidant	Inhibits inflammatory mediators; inhibits lipid peroxidation; efficient ROS scavengers; inhibits cellular signaling related to UV-mediated photoaging	Photoaging	New cosmeceutical in the market; potent anti-inflammatory and antioxidant effects

necessary for its synthesis. Vitamin C must be obtained from dietary sources (Schagen et al. 2012). Even with massive oral supplementation, the increase in skin concentration of vitamin C is limited (Manela-Azulay and Bagatin 2009).

Topical application of L-ascorbic acid is the only way to achieve significant skin levels, reaching 20–30 times higher concentrations, in comparison to orally administered vitamin C. Therefore, vitamin C has gained great popularity as a topically applied cosmeceutical.

Vitamin C is water soluble and functions in the aqueous compartment of the cell as a free radical scavenger, by donating electrons, neutralizing free radicals, and protecting intracellular structures from oxidative stress (Rahman 2007).

L-Ascorbic acid is essential for collagen biosynthesis, serving as a cofactor for prolyl and lysyl hydroxylases, enzymes that stabilize the triple helical structure of collagen. Vitamin C also influences collagen synthesis by activating its transcription and stabilizing procollagen mRNA.

Due to its anti-inflammatory properties, vitamin C has been shown to reduce erythema and inflammation after cosmetic procedures, such as laser resurfacing. It also has been shown to have skin-lightening effect (Manela-Azulay 2013).

Early formulations used vitamin C in its active form, L-ascorbic acid, and were very unstable due to the oxidation of the vitamin exposed to the air. For this reason, esterified derivatives of L-ascorbic acid have been developed to improve stability. The most common derivatives are magnesium ascorbyl phosphate and ascorbyl-6-palmitate. Magnesium ascorbyl phosphate demonstrated a skin-lightening effect in an open study. Ascorbyl-6-palmitate, which is the fat-soluble form of ascorbic acid, is not as well established in its stability and penetration and has little activity (Chiu and Kimball 2003).

Some studies suggest that the delivery of L-ascorbic acid to the skin depends on removing the ionic charge on the molecule. This is possible at a pH of less than 3.5. Concentrations higher than 20% failed to increase cutaneous absorption of vitamin C (Manela-Azulay and Bagatin 2009).

Ascorbic acid also acts as a support of other antioxidants molecules, for example, by helping in the regeneration of α-tocopherol, reducing the necessity of high ingest of Vitamin E. In this way, L-ascorbic acid also has an antioxidant power.

Topically applied vitamin C has many benefits, such as promoting collagen synthesis, lightening hyperpigmentation, and anti-inflammatory and photoprotective properties.

However, ascorbic acid has been notoriously difficult to stabilize, as it rapidly oxidizes. This may limit the topical efficacy of many of the skin care products containing vitamin C (Chiu and Kimball 2003). New developments in formulation strategies, and research confirming the benefits of vitamin C and its diverse biologic activity in the skin, make it a valuable and useful agent for the dermatologist practice (Manela-Azulay and Bagatin 2009).

Vitamin E

Vitamin E is the major lipid-soluble antioxidant in the human skin, represented by 8 molecular

forms, 4 tocopherols, and 4 tocotrienols. Vitamin E, like vitamin C, must be obtained from dietary sources. Its concentration is highest at the deepest layers of the stratum corneum.

Alpha-tocopherol is the most active form, and it is important in protecting cellular membranes from lipid peroxidation by free radicals and reducing the formation of DNA adducts and of UVA-induced sensitizing substances. Once oxidized, vitamin E can be regenerated back to its reduced form by vitamin C, which accounts for the synergistic action of these two antioxidants (Burke 2007).

Vitamin E, as alpha-tocopherol or tocopherol acetate, is used in topical over-the-counter products in concentrations ranging from 1% to 5%. In vitro studies have demonstrated the effects of alpha-tocopherol in reducing erythema and the number of epidermal sunburn cells, which are markers of skin damage related to oxidative stress caused by UVB (Manela-Azulay and Bagatin 2009).

Some esters of vitamin E (acetate, succinate, linoleate) have been shown to reduce cutaneous damage induced by UV radiation. However, alpha-tocopherol has a more pronounced photoprotective effect than its esters, which must be hydrolyzed during cutaneous absorption in order to show antioxidant activity (Andreassi and Andreassi 2003). Further, the absorption and metabolism of tocopherol acetate are highly dependent on the delivery system and formulation stability (Chiu and Kimball 2003).

Vitamin E can reduce UV-induced erythema and edema when it is applied before UV exposure. However, the use of vitamin E after sun exposure seems to have no benefit.

Topical application of vitamin E may also improve stratum corneum hydration. Another proposed mechanism of action of vitamin E is the inhibition of collagenase overexpression in aging skin.

Alpha-tocopherol also acts synergistically with vitamins A (retinol) and C (ascorbic acid) in combined products, providing enhanced photoprotection and antioxidant properties.

The incorporation of ferulic acid into a solution of 15% ascorbic acid and 1% alpha-tocopherol appears to improve the photoprotective effect and the stability of the formulation (Lin et al. 2005).

Although topical application of vitamin E demonstrates promising photoprotective and antiaging effects, specially when it is combined with other antioxidants, controlled studies in humans are needed before it can be recommended as an effective cosmeceutical agent for the treatment of both intrinsic and extrinsic aging (Manela-Azulay and Bagatin 2009).

Nicotinamide

Nicotinamide or niacinamide is a derivative of niacin (vitamin B3) and is a water-soluble vitamin part of the vitamin B group, obtained through diet. Its severe deficiency is known as pellagra.

Nicotinamide is part of the coenzymes nicotinamide adenine dinucleotide (NAD), NAD phosphate (NADP), and its reduced forms, NADH and NADPH. These molecules are important in many cellular metabolic reactions. The reduced forms act as antioxidants.

Nicotinamide is available as a component of some cosmeceutical products. It has been shown it has anti-inflammatory and anti-acne actions. It is also believed that its anti-inflammatory effect may improve skin appearance. This anti-inflammatory effect is also useful to reduce cutaneous erythema in various disorders (Manela-Azulay and Bagatin 2009).

Topical application of niacin, also known as nicotinic acid, has been limited largely due to the vasodilation and flushing it induces (Manela-Azulay and Issa 2012).

One of the mechanisms through which topical nicotinamide improves skin appearance is its action in the synthesis of sphingolipids, free fatty acids, cholesterol, and ceramides, thus decreasing transepidermal water loss. The skin-lightening effect it also exhibits is likely mediated by the suppression of melanosome transfer from melanocytes to keratinocytes.

Nicotinamide has been shown to increase collagen production in fibroblast culture, and this effect may be responsible for the improvement of skin elasticity and reduction of fine wrinkles.

All of these effects may improve skin appearance, and for this purpose, it has been used in cosmeceutical products in concentrations ranging from 3.5% to 5%.

Because it is nonirritating to facial skin, easily formulated, chemically stable, and compatible with other formulation components, niacinamide has been considered an ideal cosmeceutical agent (Manela-Azulay and Bagatin 2009).

Panthenol

Panthenol or provitamin B5 is an analog of pantothenic acid (vitamin B5). Panthenol comes in two enantiomers, D and L, but only D-panthenol (dexpanthenol) is biologically active. However, both forms have moisturizing properties.

Panthenol is a component of coenzyme A, which serves as a cofactor for a variety of enzyme-catalyzed reactions that are important in the metabolism of carbohydrates, fatty acids, proteins, gluconeogenesis, sterols, steroid hormones, and porphyrins (Ebner et al. 2002).

Dexpanthenol shows good skin penetration when topically applied in an adequate vehicle, such as water-in-oil emulsions. It is well tolerated, with minimal risk of skin irritancy or sensitization. It improves stratum corneum hydration, reducing transepidermal water loss and maintaining skin softness and elasticity. It also activates fibroblast proliferation, accelerating wound healing.

Dexpanthenol has been shown to have anti-inflammatory effects, which is useful in patients who have undergone skin surgery, therapy for burn injuries, cosmetic procedures, and for different dermatoses. It can also be used to reduce irritation provoked by tretinoin and other skin actives (Manela-Azulay and Issa 2012). Formulation containing dexpanthenol stimulates epithelization and granulation and alleviates itching.

Vitamin K

Vitamin K refers to a group of structurally similar, fat-soluble vitamins. Vitamin K1, also known as phylloquinone, phytomenadione, or phytonadione, is generally the preferred form of vitamin K.

These vitamins are present in most human tissues and participate in many cellular processes including proliferation, bone mineralization, arterial calcification, apoptosis, phagocytosis, growth control, chemotaxis, and signal transduction. Furthermore, vitamin K also has redox properties and has been shown to alter cellular metabolism, which might confer anti-inflammatory properties (Hemmati et al. 2014).

Vitamin K is essential in the process of blood coagulation and improves blood circulation, which might help the body heal the areas bruised during surgery. Topical creams with vitamin K can also help treat skin irritations, telangiectasias, stretch marks, scars, and dark circles under the eyes. It has been used in the treatment of some dermatoses, like rosacea. Furthermore, the observed increase in tensile strength by vitamin K could be due to increased collagen synthesis as well as its proper deposition and alignment.

Topical application of vitamin K has been used for the prevention of vascular manifestations of aging, suppression of pigmentation, and for the resolution of bruising. Vitamin K may facilitate the removal of extravascular blood from the skin, which accounts for its effectiveness in hastening the clearing of bruising and reducing its severity after laser treatment. Vitamin K could also improve the wound healing process due to its antioxidant properties (Hemmati et al. 2014).

However, research on vitamin K's effects on the skin is more limited than that for vitamins E and C.

Vitamin A

The human epidermis contains significant amounts of vitamin A (all-trans-retinol). Vitamin A cannot be synthesized; it must be obtained through dietary means. The ingestion of vitamin A depends on the presence of retinoids (animal sources) and carotenoids (vegetable sources) in the diet. In the body, a small percentage of retinol is converted to its

biologically active form, all-trans retinoic acid (tretinoin).

Topical retinoids have successfully been used to treat acne for nearly four decades. Initially, a retinoid was a compound of similar structure and action to retinol. Variations of this molecule have resulted in three generations of topical and systemic retinoids.

The efficacy of topical use of tretinoin in the treatment of photoaged and intrinsically aged skin is sufficiently evidence based. The effects are believed to be mediated through its binding to the nuclear retinoid acid receptors (RARs), RAR, and RXR. It induces type I and type III procollagen gene expression in the human skin, resulting in increased deposition of collagen fibrils in the dermis. It also reduces collagen breakdown by inhibiting the metalloproteinases (Manela-Azulay and Bagatin 2009).

Vitamin A, also called retinol, associates with intracellular protein that leads this nutrient to the cell's nucleus, controlling the synthesis of other proteins.

This nutrient not only stimulates glycoprotein synthesis, ensuring skin's protection and maintaining its moisture, but also inhibits high weight molecular keratin synthesis.

If there is a lack of retinol, there is a high risk of developing follicular hyperkeratosis, because there will be more high weight molecular keratin and less glycoprotein. There won't be any protection to the skin, and because of that, it will be rough and flayed.

Retinaldehyde (0.05%) is another useful topical agent for the treatment of photoaged skin. It causes less irritation but has lower efficacy than tretinoin.

Ubiquinone (Coenzyme Q10)

Ubiquinone, or coenzyme Q10, is a lipophilic antioxidant found in all human cells as a component of the aerobic respiratory chain. It is believed it may have roles in both extrinsic and intrinsic aging processes, and its levels in the skin decrease with age (Tournas et al. 2006).

In vitro studies have shown that topically applied ubiquinone helps to prevent UVA-induced damage, suppresses the expression of collagenase, and reduces fine wrinkles and other signs of skin aging (Chiu and Kimball 2003).

It has become a popular ingredient in antiaging products, even though more evidence of its efficacy is still lacking. It is believed it acts as an antioxidant, counteracting UV damage and replenishing the decreased endogenous levels of this molecule that are lost with aging.

Idebenone

Idebenone is a low-molecular-weight synthetic analog of coenzyme Q10. It is presumed to penetrate the skin more efficiently than ubiquinone.

Small clinical studies have shown that idebenone 0,5% and 1% lotions were able to reduce fine lines and wrinkles, increased skin hydration, and improved global photodamage (Farris 2007). No adverse effects were reported, and it is considered a well-tolerated compound that can be used in conjunction with other skin actives.

Limited research have shown so far that it might be one of the most potent antioxidants available on the market, but blinded, vehicle-controlled, clinical studies are still needed to confirm that hypothesis.

Green Tea Extract

Green tea is a popular beverage in many countries, made from *Camellia sinensis* leafs and buds, with known antioxidant, anti-inflammatory, and anticarcinogenic properties and appears to be beneficial when administered both orally and topically.

There are four major green tea polyphenolic catechins (GTP) in green tea extract. They are (−)-epicatechin (EC) (−)-epigallocatechin (EGC), (−)-epicatechin-3-gallate (ECG), and (−)-epigallocatechin-3-gallate (EGCG). Of these EGCG is the most abundant and the most biologically active, and it appears to be the most effective component of green tea for suppressing UV-induced carcinogenesis (Farris 2007).

GTPs are members of the flavonoid family, compounds reported to be radical scavengers, UVA absorbent, cytoprotective, anti-inflammatory, and antiapoptotic and to inhibit DNA damage and to affect cellular signaling pathways. Flavonoids act in vitro as antioxidants and induce quinone reductase activity, a marker of chemopreventive activity (Evans and Johnson 2010).

In vitro studies have shown the capacity of green tea extracts to inhibit UV-induced erythema, to reduce the number of sunburn cells, and to protect epidermal Langerhans cells, when applies before the exposure. Green tea extracts also reduced DNA damage that occurs after UV radiation, so it might be useful in mitigating the adverse effect of sunlight on the human skin (Chiu and Kimball 2003).

In view of these photoprotective effects, applying topical green tea products in the morning under sunscreen seems adequate. Green tea extract might be useful for preventing photoaging as well. EGCG has been shown to suppress metalloproteinases and age-related collagen cross-linking in mice (Farris 2007).

However, few clinical studies specifically investigating green tea extract effects on aging skin have been published to date. There is little standardization regarding concentration, and many products lack active ingredient characterization. It is generally accepted that 5% green tea extract is an effective concentration. Green tea extract is very unstable, sensitive to light and oxidation, and it is among the more difficult botanical compounds to formulate (Farris 2007).

Coffeeberry®

Coffeeberry® is a proprietary name for antioxidant harvested from the fruit of the coffee plant *Coffea arabica* and contains potent polyphenols including chlorogenic acid, condensed proanthocyanidins, quinic acid, and ferulic acid (Farris 2007).

It has been shown to upregulate the expression of collagen and downregulate the expression of metalloproteinases, resulting in improvement of fine lines, wrinkles, and skin pigmentation.

Soy Proteins (Genistein)

Soybeans are a rich source of flavonoids called isoflavones, the most potent being genistein and daidzein. Genistein is present in soy, in ginkgo biloba extract, Greek oregano, and Greek sage (Afaq and Mukhtar 2006).

Genistein has been shown to possess antioxidant, antipigmentary, and anticarcinogenic effects in the skin and to reduce the inflammatory reaction induced by UV radiation.

Studies show that genistein inhibits skin carcinogenesis and cutaneous aging induced by UV light in mice and photodamage in humans (Afaq and Mukhtar 2006).

Soy proteins can be found associated with other compounds in some cosmetic products, but strong evidence of its antiaging effects is still lacking.

Pomegranate Extract

Pomegranate (*Punica granatum*) extract is a rich source of two types of polyphenolic compounds, anthocyanidins (such as delphinidin, cyanidin, and pelargonidin) and hydrolyzable tannins (such as punicalin, pedunculagin, punicalagin, gallagic, and ellagic acid esters of glucose), and possesses strong antioxidant and anti-inflammatory properties (Afaq and Mukhtar 2006).

Studies have shown its ability to regenerate antioxidant enzymes like catalase and peroxidase. It also appears to have photoprotective action, reducing UV-induced damaged, when topically applied (Monteiro and Baumann 2012).

Further human trials and studies are necessary to understand the potentials of pomegranate as an antiaging cosmeceutical.

Alpha-Lipoic Acid

Alpha-lipoic acid (ALA) is a naturally occurring antioxidant that is both water and fat soluble. Antioxidant activity extends to both the oxidized and reduced form of ALA, dihydrolipoic (DHLA). Studies have demonstrated that both ALA and DHLA chelate metal and scavenge reactive oxygen

species, whereas only DHLA is capable of regenerating endogenous antioxidants and repairing oxidative damage. DHLA regenerates vitamin E, vitamin C, and glutathione (Farris 2007).

Lipoic acid, like other antioxidants, is unstable and difficult to formulate, and it is found in 1–5% concentration, alone or in combination with other actives.

Alpha-lipoic acid may cause a tingling sensation when applied, and some patients find it irritating. Application every other day for the first weeks may improve tolerance. Contact dermatitis has also been reported (Farris 2007).

There are few studies supporting clinical benefits for antiaging products containing ALA. It is, though, a promising anti-inflammatory agent that requires further research (Podda and Grundmann-Kollmann 2001).

Resveratrol

Resveratrol (3,5,4-trihydroxystilbene) is a naturally occurring antioxidant found in high concentrations in grapes, red wine, nuts, and some berries. It is a member of a family of compounds known as polyphenols.

Resveratrol has been the subject of intensive investigation and is reported to be a potent antioxidant, a modulator of genetic expression via signal transduction, an inhibitor of inflammatory mediators and of lipid peroxidation, and an efficient scavenger of free radicals (Baxter 2008).

Resveratrol has been demonstrated to act on cellular signaling mechanism and is related to UV-mediated photoaging, including MAP kinases, nuclear factor kappa B (NF-κB), and matrix metalloproteinases.

In vitro studies have shown that resveratrol decreases tumor incidence and delay in the onset of tumorigenesis. Topical application of resveratrol prior to UV-B irradiation resulted in a significant inhibition of UV-B-induced damage and cellular proliferation (Afaq and Mukhtar 2006).

The effect of resveratrol on photoaging requires further investigation to support clinical use.

Silymarin

Silymarin is a milk thistle plant (*Silybum marianun*) extract and contains flavonolignans, flavonoids, and other compounds. Silibinin, also known as silybin, is the major active constituent of silymarin.

Silymarin has been found to share some properties with resveratrol, including an antiapoptotic effect following UV radiation. Topical and systemic administration of silymarin was shown to attenuate burn-induced oxidative tissue injury in rats (Baxter 2008).

Due to its antioxidant and photoprotective properties, silymarin can be found in some sunscreen formulations.

However, this compound has not been extensively studied.

Lycopene

Lycopene is a carotenoid found in tomatoes and other red fruits and vegetables. Carotenoids are a family of more than 600 lipid-soluble compounds, which are naturally occurring pigments synthesized by plants.

Lycopene is considered to be the most efficient biological carotenoid singlet oxygen quencher.

Studies with oral supplementation of lycopene show it has photoprotective action and prevents UV-induced erythema. It is also reported that there is a correlation between skin roughness and lycopene concentrations in the skin (Evans and Johnson 2010).

However, there are few studies on the topical application of lycopene, even though it is commonly found in cosmetic products, like sunscreens and moisturizers.

Lutein

Lutein is a carotenoid found in leafy green vegetables, peas, egg yolks, and fruits. It has a well-established role in the eye health, acting as an antioxidant and absorbing blue light, and also has an established presence in the skin.

Some studies have shown that lutein has photoprotective, antioxidant, and hydrating effects on the skin. Oral or topical administration of carotenoids improved the measures of surface lipids, hydration, photoprotective activity, skin elasticity, and skin lipid peroxidation (Evans and Johnson 2010).

Much more research is needed on the mechanisms of action of lutein and its efficacy, when topically administered, in preventing the signs of skin aging.

Pycnogenol®

Pycnogenol® is the branded name for an extract sourced from the bark of the French maritime pine tree (*Pinus pinaster*), regarded as a powerful antioxidant, containing high concentrations of bioflavonoids and active compounds.

Studies in mice show that topical Pycnogenol® offers significant protection from UV-induced acute inflammation, immunosuppression, and carcinogenesis, when applied to the skin after daily irradiation.

Pycnogenol® in concentrations of 0,05–0,2% appears to have potential in providing photoprotection for humans in a complementary role with sunscreens (Sime and Reeve 2004).

Selenium

Selenium is an essential trace element required for the normal function of the intracellular antioxidant enzymes glutathione peroxidase and thioredoxin reductase.

Topical preparations containing selenium sulfide are frequently used to treat tinea versicolor and seborrhoeic dermatitis. However, the skin does not absorb the selenium from these preparations. Selenium can be absorbed transdermally when applied as selenomethionine (Burke 2004).

Studies have shown that, when applied topically, selenomethionine increased the minimal erythema dose and decreased UV-induced skin damage, as demonstrated by a decrease in tanning and tumorigenesis in mice (Burke 2004).

The potential applications of selenium as an antioxidant and antiaging cosmeceutical require more investigation.

Take-Home Messages

- Under physiological conditions, human skin possesses different antioxidant mechanisms that prevent cellular damage from severe oxidative stress. However, the levels of these antioxidants are reduced by age and exposure to environmental stress, such as ultraviolet radiation, tobacco smoke, alcohol consumption, and pollution.
- Topically applied antioxidants are an important group of cosmeceutical agents capable of preventing and reducing UV-induced skin damage, by protecting skin cells against the action of ROS. Antioxidants may be combined with other actives, resulting in complementary mechanisms of action to prevent skin aging.
- Antioxidants are notoriously unstable, so care must be taken during formulation to ensure they don't become oxidized and inactive.
- Vitamin C is the most abundant antioxidant in the human skin. New developments in formulation strategies, and research confirming the benefits of vitamin C and its diverse biologic activity in the skin, make it a useful agent for the dermatologist practice.

Cross-References

- ▶ Approach in Photodamaged Skin, Melasma, Acne, and Rosacea
- ▶ Chemical and Physical Sunscreens
- ▶ Evaluation and Classification of Aging
- ▶ Oral Photoprotection
- ▶ Photoprotection: Concept, Classification, and Mechanism of Action
- ▶ Skin Anatomy, Histology, and Physiology

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Antiglicants

Paulo Notaroberto

Abstract

There is remarkable evidence among scientific literature that the glycation with the consequence formation of advanced glycation end products (AGEs) participates directly and indirectly (enhancing oxidative stress by stimulating ROS concentration and activity) on the aging process. In the skin, deleterious effect of AGEs is enhanced by UV exposure in sun-exposed areas. Today, glycation treatment is mainly based on preventing AGE formation but AGE scavenger products are being studied. The most promising data refer to studies for the treatment of diabetes. One can suggest the same approach for skin aging as in diabetic subjects by analogy, but the fact is that there are few significant references that support anti-glicants for lowering the aging rate. "Antiglicants" chapter presents the glycation formation of advanced glycation end product (AGE) theory for aging and its correlation with others theories mainly the theory of oxidative stress and the formation of free radicals (reactive species of oxygen – ROS). The most used and promissory therapeutic approaches are discussed.

Keywords

Glycation • Anti-glycants • Advanced glycation end products • Aging • Skin aging • Diabetes • Reactive species of oxygen

Contents

Introduction

The study of the aging process has gained great interest in the last decades because of the fact that life expectancy is increasing substantially (Pageon et al. 2007). Furthermore, many billions of dollars are spent annually on face care products claiming to treat and protect against skin aging (Hughes et al. 2013). The industry of beauty in Brazil is the third biggest in the world losing to the USA and Japan (Martins et al. 2013). Aging can

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be defined as an insidious, dynamic, and progressive complex process that leads to morphological, functional, biochemical, and psychological modifications on the subject which impacts negatively on the adaptability to the environment causing greater vulnerability and higher incidence of pathological processes that eventually causes death (Nascimento 2015). Skin aging is a result of internal processes (intrinsic aging) and the cumulative results of aggressive actions from the external environment, such as sun exposure (UV radiation), tobacco, stress, and pollution.

Extrinsic skin aging most remarkable histological findings are epidermal thickening, atypical keratinocytes, and reduced collagen in dermis with abnormal elastin (elastosis) in papillary dermis (see chapter "▶ Skin Anatomy, Histology, and Physiology"). Clinical manifestations are characterized by loss of elasticity and dry, wrinkled, and patchily pigmented skin (Hughes et al. 2013). Extrinsic skin aging is potentially feasible to be prevented once external aggressions are easier to be identified and, consequently, avoided. Hughes and her group conducted a prospective clinical trial in Australia involving 903 adults younger than 55 years for 4.5 years and concluded that regular sunscreen use retards skin aging in healthy middle-aged men and women (Hughes et al. 2013).

Intrinsic skin aging is featured by dermal matrix changes marked by thinning and loss of elasticity (Pageon et al. 2007) leading to wrinkle formation and a sagging skin. Clinical manifestations observed during skin aging are the result of a wide and complex process that despite being widely studied is not fully understood yet. It comprehends multiple chemical reactions and biochemical alterations that occur independently but also can interact among themselves and boost each other. Until today, more than 300 mechanisms and theories to explain the cellular aging process have been proposed, and the decreased proliferative capacity and telomere shortening, mitochondrial DNA single mutations, and free radical theory (Gkogkolou and Bohm 2012) are the most studied and mentioned in the literature. Extracellular matrix alterations are also observed during the intrinsic skin aging process and are mainly a result of oxidative stress, inflammation, impairment of cellular (fibroblast) function, and glycation.

The oxidative stress theory, also known as free radical theory of aging, was first described in 1956 (Declercq et al. 2009) and is based on the loss of balance between the high concentration of reactive oxygen species (ROS) that cause oxidative damage and the innate ability of ROS scavenging. ROS accumulation reacts in several extracellular matrix, membranes, and cellular sites promoting not only tissue and cellular damages but also triggering and maintaining inflammation. Local inflammatory response contributes to structural changes observed in aged skin because of the impairment of the immune response, matrix metalloproteinase (MMP) activation, and pro-inflammatory cytokine production (Gkogkolou and Bohm 2012).

Briefly, glycation is a nonenzymatic reaction that takes place between free amino groups in proteins (lysine and arginine side groups) and a reducing sugar such as glucose leading to the formation of advanced glycation end products (AGEs) (Pageon et al. 2013). AGEs of cellular proteins are said to be possible basic components of the "master biological clock" (Severin et al. 2013). In the recent years, the study of glycation is getting more importance in the skin aging etiology, and anti-AGE strategies have received high interest from pharmaceutical companies for the development of novel antiaging cosmeceutical compounds (Gkogkolou and Bohm 2012).

Glycation

Maillard Reaction and Age Production

Maillard reaction is a nonenzymatic process firstly mentioned by Maillard in 1912 (Louis Camille Maillard, 1878–1936) characterized by the reaction between reducing sugars and amino acids in solution producing dark yellowish-brown colored products called melanoidins (Severin et al. 2013; Vistoli et al. 2013). Glycation is also known as nonenzymatic glycosylation, but it must be clearly distinguished from glycosylation, which is an enzymatic reaction. John E Hodge described in 1953 that the sugar aldehyde group reacts with amino groups of amino acids (especially of basic

lysine and arginine residues) producing a non-stable Schiff base N-glycosides at the initial stage of glycation (Gkogkolou and Bohm 2012; Severin et al. 2013; Hodje 1953). N-glycosides undergo a rearrangement that leads to formation of a more stable ketoamine (1-amino-1-deoxy-ketoses) called Amadori products, or Amadori compounds (Gkogkolou and Bohm 2012; Severin et al. 2013). At this stage, the process is still reversible for the Schiff bases as well as for the Amadori products (Gkogkolou and Bohm 2012). The Amadori products undergo dehydration, polymerization, oxidation, and oxidative breakdown to form more stable advanced glycation end products (AGEs) (Gkogkolou and Bohm 2012; Sadowska-Bartosz and Bartosz 2015). Dicarbonyl products, glyoxal and methylglyoxal, are formed as intermediate products in the course of the Maillard reaction. These highly active compounds are also formed inside cells, as by-products of glycolysis. They can react with proteins producing intra-protein and inter-protein cross-links resistant to the action of enzymes (Severin et al. 2013; Sadowska-Bartosz and Bartosz 2015). AGEs are highly stable and the process of glycation is irreversible from this point.

AGEs in the Skin

AGEs are a very heterogeneous group of molecules and can be detected in almost all tissues of the human body. Carboxymethyllysine (CML), a nonfluorescent protein adduct, was first described by Ahmed in 1986 and is the most prevalent AGE in vivo (Gkogkolou and Bohm 2012; Sadowska-Bartosz and Bartosz 2015; Ahmed et al. 1986; Reddy et al. 1995). CML is present in epidermis (Kawabata et al. 1814), aged and diabetic dermis, and photoaging-actinic elastosis (Dyer et al. 1993; Jeanmaire et al. 2001). Main targets of the CML on skin are the epidermis (stratum corner, stratum granulosum, and stratum spinosum), collagen, elastin, and vimentin (Kawabata et al. 1814; Dyer et al. 1993; Jeanmaire et al. 2001).

Pentosidine is composed of an arginine and a lysine residue cross-linked to a pentose. It is a fluorescent glycoxidation product, forms protein-protein cross-links, and is found in the collagen of aged and diabetic dermis (Gkogkolou and Bohm 2012).

Dicarbonyl compounds such as glyoxal, 3-deoxyglucosome, and methylglyoxal are highly reactive molecules and lead to protein cross-links, particularly in the aged dermis collagen. Glucosepane, carboxymethyl-hydroxylysine, carboxyethyl-lysine (CEL), fructose-lysine, methylglyoxal-derived hydroimidazolones, and pyrraline form nonfluorescent protein adducts, while glyoxal-lysine dimer (GOLD) and methylglyoxal-lysine dimer (MOLD) form nonfluorescent protein cross-links leading to collagen impairment on the aged dermis (Gkogkolou and Bohm 2012).

AGE Formation

Certain kinds of food, such as glucose syrup, toffee, and caramel, are exogenous sources of AGEs. AGEs can also be entirely produced endogenously at low rates by the normal metabolic process of the organism, but AGE formation can be enhanced in pathological conditions as it is seen in diabetes. Just as increased concentration of reactive oxygen species (ROS) causes oxidative stress, increased levels of sugars (glucose, fructose, deoxyglucose, and triose phosphates) and reactive dicarbonyl compounds (glyoxal and methylglyoxal) can result in high formation of AGEs (Severin et al. 2013; Sadowska-Bartosz and Bartosz 2015). Oxygen, reactive oxygen species (ROS) , and redox-active transition metals accelerate AGE production and form the so-called advanced glycoxidation end products (Gkogkolou and Bohm 2012; Jedsadayanmata 2005), such as CML and pentosidine (Pageon et al. 2013). The UV effect on AGEs (like pentosidine) generates ROS in the extracellular matrix (Pageon 2010). Pageon performed an experiment that demonstrates CML and pentosidine accumulation in sun-exposed skin (Pageon et al. 2013). UV exposure triggers a vicious circle of glycoxidation and ROS formation, and it is more marked in aged skin compared to young skin (Pageon et al. 2013). Nomoto

conducted a clinical trial where 244 Japanese aged from 20 to 59 years old (82 men and 162 women) answered a questionnaire about lifestyle behavior and were submitted to skin analysis by measurement of autofluorescence (several AGEs are fluorescents) on the upper arms. Smoking and alcohol intake were positively correlated to skin autofluorescence as well as few sleeping hours (Nomoto et al. 2012). Finally, circulating AGE levels seem to be genetically determined, as shown in a cohort study of healthy monozygotic and heterozygotic twins (Gkogkolou and Bohm 2012).

The content of AGEs in the organism is a result of the rate of their formation and the capacity of removing. Many cells have developed intrinsic enzymatic detoxifying pathways against accumulation of AGEs (Gkogkolou and Bohm 2012).

Mechanisms of Action

Once AGE formation is irreversible, the concentration is proportional to the protein turnover rate. Therefore long-lived proteins are prone to be mainly modified by glycation (Gkogkolou and Bohm 2012; Vistoli et al. 2013). Collagen types I and IV have a slow turnover rate of about 10 years, and other dermal long-lived proteins like fibronectin are severely compromised from glycation during intrinsic chronological aging (Dyer et al. 1993; Jeanmaire et al. 2001). The appearance of glycated collagen is first observed at the age of 20. It accumulates with a yearly rate of about 3.7% reaching a 30–50% increase at 80 years of age (Gkogkolou and Bohm 2012; Jeanmaire et al. 2001).

AGEs can be generated and accumulated intracellularly and extracellularly. Extracellular matrix (ECM) proteins are highly affected. Collagen type I is the most abundant collagen in the skin and is responsible not only for resistance and skin architecture but also performs an active component being able to interact with cells affect various cell functions such as migration, differentiation and proliferation (Gkogkolou and Bohm 2012). Collagen type IV is located in the basal membrane. Collagen function is impaired by glycation in various ways. Intermolecular cross-links of adjacent collagen fibers change its biomechanical properties leading to stiffness and decreased flexibility. There are charge changes, and the formation of AGEs on side chains of collagen prevents its binding and interaction with cells and other matrix proteins, inhibiting its ability to react (Gkogkolou and Bohm 2012; Vistoli et al. 2013). Modified collagen is resistant to degradation by MMPs, thus inhibiting its removal and replacement by newly synthesized and functional one resulting in impairment of the collagen turnover (Paul and Bailey 1996). Elastin and fibronectin glycation plays an important role on decreased skin elasticity found in diabetic subjects and aged skin. CML-modified elastin is more resistant to proteolytic degradation, and it is found almost exclusively in sites of actinic elastosis and not in sun-protected skin highlighting its potential role in photoaging (Gkogkolou and Bohm 2012; Declercq et al. 2009; Pageon et al. 2013).

The intermediate filament vimentin seems to be the major site of glycation in human dermal fibroblasts (Kueper et al. 2007) and CK10 and nuclear factor-kappa B (NF-kB) in keratinocytes (Kueper et al. 2007; Tiang et al. 2012). Cytoskeletal and intracellular proteins including enzymes and growth factors can be target for AGEs impairing the main cellular functions such as migration, cellular division, and collagen synthesis. DNA and lipids can be glycated compromising cell membranes and cell functioning (Gkogkolou and Bohm 2012).

RAGE is by far the most studied AGE receptor. It is a multi-ligand membrane receptor of the immunoglobulin family (Severin et al. 2013) and is present in epidermal keratinocytes, dermal fibroblasts, endothelial cells (Gkogkolou and Bohm 2012), and macrophages (Severin et al. 2013). AGE receptors in macrophage surface were originally assumed to bind and neutralize AGE. However, further studies showed that this binding triggers oxidative stress and activates the NF-kB factor leading to an inflammatory response, oxidative stress (Severin et al. 2013), decreased cell proliferation, induced apoptosis, and increased MMP production (Gkogkolou and Bohm 2012).

Recently, Miyata proposed that AGEs inhibit mesenchymal-epidermal interaction by upregulating proinflammatory cytokines in hair follicles, and it seems to accelerate the onset of androgenetic alopecia as well as senescent alopecia (Miyata et al. 2015).

AGEs have been etiologically implicated in aging and aging-related pathologies so their use as biomarkers is near the reality. Until now it has been shown that skin autofluorescence positively correlates with various diabetes and age-related complications. Skin glycation has been proposed as a prognostic factor for the development of diabetic complications. Lately it was shown that skin autofluorescence increases with chronological aging and correlates with skin deposition of AGEs, making this method a potential tool in investigating the effect of various antiaging products of the cosmetic industry (Gkogkolou and Bohm 2012).

Anti-glycants

With the growing knowledge about the importance of AGEs on the pathogeny of diabetes and aging, the development of preventing and treating strategies against AGEs became of great interest among scientific community.

Aminoguanidine, a nucleophilic hydrazine, is a therapeutic agent that reacts rapidly with dicarbonyl compounds such as methylglyoxal, glyoxal, and 3-deoxyglucosone preventing AGE formation (Thornalley 2003). It has no effects on more advanced stages of glycation. Despite its potential effects in attenuating various diabetes- and age-related complications in animal models, its use in clinical practice is limited due to adverse effects in clinical trials with diabetic patients. In an in vitro skin aging model, it could attenuate collagen glycation; however, its effects against AGE-induced collagen modification in vivo have been contradictory. There are no consistent data supporting topical application of aminoguanidine in the skin (Gkogkolou and Bohm 2012; Sadowska-Bartosz and Bartosz 2015). Aminoguanidine is used as a reference inhibitor of glycation on in vitro assays (Gasser et al. 2011).

Pyridoxamine, a naturally occurring vitamin B6 isoform, seems to present a variety of chemical properties, including the scavenging of free radical species (ROS) and carbonyl species formed in sugar and lipid degradation and chelation of metal ions that catalyze Amadori reactions. It has shown promising results in a phase II clinical trial against diabetic nephropathy. Oral intake of pyridoxamine resulted in potent inhibition of skin collagen CML formation in diabetic rats, but its potential against skin aging remains to be shown (Gkogkolou and Bohm 2012; Sadowska-Bartosz and Bartosz 2015).

Anti-type 2 diabetes drugs such as metformin and pioglitazone have anti-glycation effect by lowering blood glucose. From among other drugs in use, angiotensin receptor blockers, inhibitors of angiotensin converting enzyme, and pentoxifylline were also found to inhibit AGE formation. Other inhibitors of protein glycation include antioxidants, such as vitamin C and vitamin E, green tea, and metal ion chelators (deferoxamine and penicillamine). Aspirin inhibits glycation competitively by capping amino groups. Amadori products already formed may be deglycated by enzymes called amadoriases. A group of compounds has been discovered, which break α-dicarbonyl cross-links, among them phenacylthiazolium bromide and its stable derivative dimethyl-3-phentayl thiazolium chloride (ALT-711) (Gkogkolou and Bohm 2012; Sadowska-Bartosz and Bartosz 2015).

Pomegranate (*Punica granatum L.*) extract acts as a free radical scavenger, and its anti-glycation ability was demonstrated by lowering the rate of AGE formation and it also inhibited the formation of fructosamine in vitro (Rout and Banerjee 2007). Yagi et al. conducted a prospective study with ten postmenopausal females receiving oral administration of 100 mg/day of pomegranate extract for 12 weeks and noted that all subjects demonstrated a decrease in the glycative stress (Yagi et al. 2014).

Scientific studies showed that active ingredients extracted from the roots of *Pueraria lobata* (active ingredient: puerarin, an isoflavone) and from the leaves of *Eucommia ulmoides* (active

ingredient: chlorogenic acid, an acid–phenol) have protective activity against glycation. These ingredients proved to be able to reduce the level of blood glucose in diabetic rats and to decrease the content in AGEs (Gasser et al. 2011). Arbutin, a naturally occurring compound with an anti-oxidative property, inhibits glycation in vitro (Jedsadayanmata 2005). Red grape skin extract demonstrated a protective effect against fructose-mediated protein oxidation in vitro lowering the AGE fluorescence intensity and the level of fructosamine (Jariyapamornkoon et al. 2013).

Carnosine is an endogenous dipeptide, composed of β-alanine and L-histidine, and it occurs naturally in some species of vertebrates, including humans. When provided to humans as a supplement, carnosine has antioxidant properties, acting against free radicals. Carnosine scavenges both reactive oxygen and nitrogen, which contain unpaired electrons, and also creates complex chemical compounds with zinc and copper ions (Buzden and Rymaszewska 2013; Hipkiss 2009). Carnosine dipeptide may inhibit lipid oxidation through a combination of free radical scavenging and metal chelation. Babizhayev demonstrated that the use of oral non-hydrolyzed carnosine and carcinine for a period of 3 months improved the overall appearance of the skin and reduced the wrinkles (Babizhayev et al. 2012). In mice that underwent laboratory-accelerated aging, carnosine administration prolonged life expectancy and improved characteristics of their physical appearance and behavior (Buzden and Rymaszewska 2013). Carnosine proved to have an anti-glycation effect and inhibit secondary complications associated with diabetes (Buzden and Rymaszewska 2013; Hipkiss 2009).

The blueberry extract, an AGE inhibitor, and C-xyloside, an glycosaminoglycan synthesis stimulator, were used topically for 12 weeks in female diabetic subjects. This treatment resulted in significant improvement of skin firmness, wrinkles, and hydration although it failed to show a significant decrease in the cutaneous content of AGEs (Draelos et al. 2009).

A severe restrictive diet may not be feasible. However, dietary intake of AGEs correlates with serum AGEs and can induce systemic oxidative stress, increase RAGE expression, and decrease antioxidant levels and life span in mice (Gkogkolou and Bohm 2012). There are no studies investigating the effects of AGE-poor diets on skin aging in humans. Meanwhile, it has been shown that skin collagen glycation positively correlates with blood glucose levels in diabetes and that intensive treatment can reduce the levels of skin glycation, implicating that a diet low in AGEs may have a beneficial effect on skin glycation (Gkogkolou and Bohm 2012).

Topical 5% niacinamide (vitamin B3) provides a variety of beneficial effects to skin, such as improvement in the appearance of facial skin texture, fine lines/wrinkles, hyperpigmentation, red blotchiness, and yellowing (sallowness). Niacinamide acts as a precursor of NAD(P) coenzyme and has been shown to increase NADPH levels in aged skin cells. While this coenzyme precursor role for niacinamide may explain in general how it can have multiple effects on clinical appearance and function of skin, the precise mechanism of action remains unknown. For skin yellowing which is at least in part because of the oxidative protein glycation process, a niacinamide-induced elevation of the endogenous antioxidant NAD(P)H level would be expected to modulate the yellowing phenomenon (Bisset et al. 2004). An anti-glycation effect for niacinamide has been reported by Griffiths and Weiss (Griffiths and Voorhees 1993; Weiss et al. 1988).

Conclusion

There is remarkable evidence among scientific literature that the glycation with the consequence formation of advanced glycation end products (AGEs) participates directly and indirectly (enhancing oxidative stress by stimulating ROS concentration and activity) on the aging process. In the skin, deleterious effect of AGEs is enhanced by UV exposure in sun-exposed areas. Today, glycation treatment is mainly based on preventing AGE formation but AGE scavenger products are being studied. The most promising data refer to

studies for the treatment of diabetes. One can suggest the same approach for skin aging as in diabetic subjects by analogy, but the fact is that there are few significant references that support anti-glicants for lowering the aging rate.

Take-Home Messages

- Glycation with the consequence formation of advanced glycation end products (AGEs) participates directly and indirectly (enhancing oxidative stress by stimulating ROS concentration and activity) on the aging process.
- In the skin, deleterious effect of AGEs is enhanced by UV exposure in sun-exposed areas.
- AGEs have been etiologically implicated in aging and aging-related pathologies.
- The content of AGEs in the organism is a result of the rate of their formation and the capacity of removing.
- Many cells have developed intrinsic enzymatic detoxifying pathways against accumulation of AGEs.
- There are few significant references that support anti-glicants for lowering the aging rate.

Cross-References

- ▶ Approach in Photodamaged Skin, Melasma, Acne, and Rosacea
- ▶ Chemical and Physical Sunscreens
- ▶ Evaluation and Classification of Aging
- ▶ Oral Photoprotection
- ▶ Photoprotection: Concept, Classification, and Mechanism of Action
- ▶ Skin Anatomy, Histology, and Physiology

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Cosmeceutical Ingredients: Botanical and Nonbotanical Sources

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Abstract

Cosmeceuticals are considered to be all products containing biologically active substances and ingredients with beneficial effects on the skin, interfering positively on skin physiology, without therapeutic pretension, but may have preventive effects beyond beautification. Thirty-five percent of US dermatologists already include cosmeceuticals in their prescriptions, and since then cosmeceutical has represented constantly expanding group. In addition, it is certain that it is up to dermatologists to carefully evaluate each patient and the correct indication and need for the use of such substances. Although not individualized in a particular category, according to the American standards defined by the FDA, cosmeceuticals should always be evaluated to have checked their safety and efficacy profiles, since these are created with pharmacologically active substances that must respect certain pharmacokinetic principles, as they reach the deeper layers of the skin.

Keywords

Cosmetics • Antioxidants • Retinoids • Fatty acids

Contents

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Introduction

Cosmeceuticals represent an expanding class of products; in fact, about 90% of all cosmetics sold in the world are cosmeceuticals (Brody 2005). In the USA, 35% of all dermatologists already include cosmeceuticals in their prescriptions (Brody 2005). Considering the spontaneous demand for this type of product, 40% of cases or patients seek cosmeceuticals to obtain any skin rejuvenation benefit (Brody 2005).

In relation to market share, moisturizers correspond to 33% of all products sold, followed by 14% of products for eyes area, and, finally, by sanitizers, which correspond to 13% (Brody 2005). This market moves billions of dollars, what makes dermatologists to encourage companies to launch products with scientific productions of high quality, allowing them to properly evaluate the benefits obtained when those products are used (Brody 2005).

Kligman firstly introduced the term "cosmeceutical" in 1984 (Graham and Kligman 1984). However, it is possible to meet different other synonyms, such as dermaceuticals, active cosmetics, and functional cosmetics (Draelos 2014).

According to the FDA (Food and Drug Administration, USA), cosmeceuticals are not individualized in a specific category; the term "cosmeceutical" has no specific meaning under the law (Draelos 2005). From a dermatological point of view, cosmeceuticals are considered as products containing biologically active substances and ingredients with beneficial effects on the skin, interfering positively on skin physiology (Draelos 2005; Kligman 1995). Cosmeceuticals have no therapeutic claims, but may have preventive effects beyond beautification (Kligman 2005).

For a cosmeceutical to act as expected, it should act not only on the stratum corneum but also being able to reach deeper layers of the skin (Kligman 2005). To be considered a cosmeceutical, a product must respect some dermatological pharmacokinetics, which are (Kligman 2005):

1. Dissolution of the active substance in the vehicle in question.
2. Complete coverage of the skin surface when applied.
3. Partition of the active substance in the stratum corneum.
4. Permeation of the active substance through the entire thickness of stratum corneum.
5. Partition on hydrolipidic epidermal component.
6. Migration throughout the epidermis.
7. Substance removal through either metabolism or via vascular system.

The efficacy and safety of these products are being increasingly questioned and studied (Brody 2005; Draelos 2005, 2014). Whenever possible, the effectiveness of actives and vehicles present in the formulation should be evaluated (Brody 2005; Draelos 2005, 2014). Usually there is needed to study the products for a 3-month minimum period to differentiate the efficacy of the vehicle versus the efficacy of the active ingredient; in order to determine if the observed results were not dependent on the vehicle present in the formulation – such as differentiating if the skin softness that can be afforded by the vehicle or by the presence of certain active moisturizer (Draelos 2014).

Basic Concepts

Cosmetology, the science of cosmetics, is multidisciplinary as it encompasses in addition to Dermatology, Physics, Chemistry, Physiochemistry, Physiology, Histology, Biochemistry, among others (Draelos 2014).

The desire to maintain skin youthfulness and treat aged skin or unaesthetic skin changes is leading to the increasing use of cosmeceuticals (Draelos 2014). Both physical (with great sensory

impact) and chemical aspects of cosmeceuticals influence directly on the effectiveness of such products (Barnes 2000). The physical aspects of viscosity, consistency, and flow properties are important in the manufacture process of cosmetics and cosmeceuticals (Brummer 2006). These directly influence the immediate acceptance by the user, who considers sensory issues, such as the spreadability and texture, the basic precepts for immediate acceptance of the product (Barnes 2000; Brummer 2006; Almeida and Bahia 2006; Laba 1993).

The successful development of a new product relies on the choice of active ingredients (Laba 1993). Agitation is the component incorporation method that of the product and it is from this that emulsions, solutions, dispersions, suspensions, pastes, or solid powders arise (Brummer 2006). Grinding is another important process in the transformation of the raw material in smaller particles, used in makeup for incorporating pigments (Barnes 2000; Brummer 2006; Almeida and Bahia 2006; Laba 1993). Packaging is another important part of the final product, since the right packaging ensures the maintenance of the product characteristics (Barnes 2000; Brummer 2006; Almeida and Bahia 2006; Laba 1993).

The cosmetic and cosmeceutical formulations are composed of two main parts: the structural portion (vehicle) and functional portion (actives) (Brummer 2006). The combination of the raw materials used for the effectiveness of the product should be evaluated (Barnes 2000; Brummer 2006; Almeida and Bahia 2006; Laba 1993). Each raw material should be known individually and which have synergistic effects of its chemical combination to ensure the stability of the final product throughout its shelf life (Brummer 2006). The electric charge of each substance, as well as its pH, are important for the development of a Cosmeceutical (Barnes 2000). If no physicochemical affinity between the structural and functional components is found, the final result will likely be an unstable and ineffective formulation (Brummer 2006).

Emulsion is used in preparing the main cosmeceutical, being the basis for the formation of this interaction between the emulsifiers: oil and water (Brummer 2006; Almeida and Bahia 2006). Emulsification is defined by the thermodynamically stable dispersion of two immiscible liquids, usually a polar and the other nonpolar, in which one introduces into droplets (disperse phase) and the other is the dispersion medium (continuous or external phase) (Brummer 2006). In practice, there must be a third component called an emulsifier (Brummer 2006). The emulsifiers may have a greater or lesser tendency to be solubilized hydrophilic in oily or aqueous medium, depending on their hydrophobic and hydrophilic groups (Brummer 2006). If the emulsifier tends to be soluble in water, it is useful for the formation of oil in water emulsions (O/W) (Almeida and Bahia 2006). On the other hand, if its characteristic dominate is nonpolar, preferably being dissolved in an oily medium, will be useful in formation of oil in water emulsions (W/O) (Almeida and Bahia 2006).

Rheology, from the Greek *rheo* (which means "flow"), relates to the study of the flow of solid deformation and fluidity of liquids (Laba 1993). Rheological components determination of formulation is ultimately related to the detection of stability of active principles in the product (Laba 1993). The study of the rheological properties must be made during product development and quality control, as it influences the pattern of use, acceptance, and product quality (Barnes 2000). The rheological study may be applied with one initial step in the evaluation of sunscreens, for example, wherein formulations containing sunscreens should provide flow characteristics with film formation on skin (Gaspar and Maria Campos 2003). Sunscreens are designed to keep the active compounds on the stratum corneum and not to penetrate into deeper layers. This provides exposure to the sun and protects against potential immunological reactions.

Texture represents a set of physical properties that keeps sensory perception as a consequence of the internal structure of the material (Jones and Woolfson 1997). It can be subjectively evaluated by sensory measurements and also through instrumental measurements (Jones and Woolfson 1997). The textural and mechanical properties of

an emulsion depend on the constituents of the formulation and the interaction between the continuous and dispersed phase (Jones and Woolfson 1997).

Hardness and adhesiveness are dependent characteristics on cohesive forces and viscosity of the formulation (Lachman et al. 2001). They are inversely proportional, since greater interaction between the molecules leads to greater strength and toughness (Lachman et al. 2001).

The texture and product application characteristics are fundamental parameters for adherence to product use. Therefore, it is essential to carry out the analysis of cosmeceutical texture formulations profiles in parallel to the study of the rheological behavior of topical products (Jones and Woolfson 1997; Lachman et al. 2001).

The main components of a cosmeceutical formulation are (Lachman et al. 2001):

1. Water, as the main and major product, should be pure and free from microorganisms.
2. Ethyl alcohol, used in alcohol-water mixtures, as part of the vehicle applied to solubilize various raw materials.
3. Humectant, a substance able to retain water in the formulation.
4. Field grease, oils, and waxes used as emollients and thickeners.
5. Hydrophilic thickener, which are raw materials from synthetic vegetable origins or biotechnology, capable of swelling in the presence of water, as a gel.
6. Surfactant, a substance with a detergent feature over greasing, thickener, and foam producer.
7. Preservative, antimicrobial, and antioxidant.
8. Dye, to impart color.
9. Fragrance, gives a pleasant odor and used to mask characteristic odors.

The chemical stability and shelf life is important for effectiveness and safety. A product degradation curve should be made (Leonardi and Maria Campos 2001). The validity period is set as the maximum time after preparation of the product and under certain storage conditions, during which the formulation shows no degradation exceeding 10–15% (Levine 1995). The long-term studies in environmental conditions are fundamental to establish the actual expiration date (Levine 1995).

There is a mathematical determination equation that supports validity, called Arrhenius Equation, which takes into account the chemical kinetics of degradation of the active substances (Leonardi and Maria Campos 2001; Levine 1995; Maria Campos 2002). Chromatography can also be used; it separates the active substances from its degradation products (Maria Campos 2002).

Cosmeceutical Classes

Antioxidants

In 1956, Harman and col. first proposed the importance of the participation of free radicals in the aging process: they were divided into intrinsic (formed by cellular metabolism itself) and extrinsic (produced by exogenous factors – ultraviolet radiation, smoking, alcohol, and pollution) products. This theory is quite consolidated and accepted today (Florez-White 2013).

Free radicals are reactive oxygen species (ROS) with unpaired number of electrons that can damage cell structures such as DNA, proteins, and membranes (Costa 2012). Under normal circumstances, ROS are neutralized by endogenous antioxidant defense systems, either enzymatic (superoxide dismutase – SOD, catalase, and glutathione peroxidase) or nonenzymatic (vitamin E, vitamin C, glutathione, and ubiquinone), that work in a coordinated manner (Florez-White 2013). However, as part of the natural aging process added to the oxidative stress caused by environmental factors, there is an imbalance between endogenous defense mechanisms with increased production of ROS, resulting in skin aging (Florez-White 2013).

Regarding this theory, it is intuitive to think that the topical application of antioxidants could neutralize some of the free radicals produced in the process, reducing or preventing, at least in part, signs of aging skin (Leonardi and Maria Campos 2001; Costa 2012). To have effectiveness

Table 1 Antioxidant classification according to its solubility with the most important examples from each subtype

Hydrophobic	Vitamin E
	Ubiquinone (coenzime -Q10)
	Idebenone
	Lycopene
	Curcumin
Hydrophilic	Vitamin C
	Glutatihone
	Green tea – epicatechin derivatives
	Silimarin
	Caffea arabica and CoffeBerry extract
	Polipodium leucotomas
	Resveratrol
	Grape seed extract
	Pomegranate extract
Other antioxidants	Pycnogenol
	Niacinamide
	Selenium

using topical administration of antioxidants, it should be taken into account the stability of the product, as well as pH and appropriate vehicle, beyond its absorption through the skin still in active form, remaining long enough to achieve the desired effects (Leonardi and Maria Campos 2001; Costa 2012). Recent research suggests that different combinations of antioxidants have a synergistic effect and are thereby more effective, compared with the single use of some substances (Florez-White 2013). It is observed that some data also suggest some cumulative or additive benefit in concomitant oral and topical antioxidant products (Florez-White 2013).

From now, it is going to be covered the main antioxidants in cosmetic formulations currently marketed. From the point of view of its solubility, they are classified according to Table 1.

Hydrophobic Antioxidants

- Vitamin E (tocopherol): alpha-tocopherol is the isoform with the greatest activity (Costa 2012). Its main function is to protect cell membranes from oxidative stress, by reducing the lipid peroxidation (Florez-White 2013; Costa 2012). It reduces photoaging and photocarcinogenesis (Florez-White 2013; Costa 2012) and inhibits the formation of thymine dimers and ciclopirimidine induced by ultraviolet radiation, which gives photoprotective effect (Costa 2012). It also inhibits melanogenesis through tyrosinase inhibition. The association of vitamin E with vitamin C increases its antioxidant power, since vitamin C regenerates vitamin E oxidized sites on lipid peroxidation, giving greater stability to the molecule and increasing their photo protective effect (Florez-White 2013). **High concentrations of vitamin E have been associated with bleeding complications.**
- Coenzyme Q10 (ubiquinone): It is an antioxidant found in all human cells as a component of the respiratory chain. It is found in a lesser extent in aged skin compared to youthful skin (Florez-White 2013). In vitro CoQ10 suppresses the expression of collagenase after exposure to ultraviolet radiation A (Costa 2012). There are few studies on the effect of topical application, but it appears to reduce the clinical score of wrinkles and gives a rejuvenated appearance to the skin, being present in various formulations in over the counter cosmetics (Florez-White 2013).
- Lycopene: carotenoid antioxidant without pro-vitamin A action found in fruits and vegetables (mainly tomatoes), responsible for its reddish color (Florez-White 2013). It stimulates the division of the keratinocytes and controls the differentiation (Costa 2012). Although there is little clinical data of the product, it is included in many products for skin care, such as moisturizers and sunscreens (Costa 2012).

Hydrophilic Antioxidants

- Vitamin C (ascorbic acid): is a water-soluble vitamin found in citrus fruits and leafy dark green color vegetables (Florez-White 2013). It is involved in several cellular reactions, most often as a cofactor providing electrons necessary for reducing molecular oxygen and neutralizing free radicals in the aqueous compartments of the skin (Florez-White 2013; Costa 2012; Bagatin 2009). It also plays an important role in the regeneration of vitamin E, with great synergistic effect between the two molecules, especially in

photoprotection (Florez-White 2013; Bagatin 2009). It is essential in the synthesis of collagen and elastin, producing collagen more stable and less sensitive to heat (Florez-White 2013; Costa 2012). It also reduces hyperpigmentation by inhibiting tyrosinase and improves barrier function of the epidermis to stimulate the production of sphingolipids (Costa 2012). Topical application of ascorbic acid gives a photoprotective effect demonstrated by the reduction in erythema after radiation and decrease in the number of sunburn cells (Florez-White 2013; Costa 2012). To be effective and be able to penetrate the stratum corneum, the molecule must lose its ionic charge, as well as have a pH below 3.5 and a concentration between 15 and 25% (Costa 2012).

- Green tea: is extracted from the plant *Camellia sinensis* and has a recognized antioxidant, anti-inflammatory, and anticancer effects (Florez-White 2013; Bagatin 2009). Its derivatives, the epitechins or polyphenols, in particular 3-epigallocatechin gallate (EGCG), is its constituent with largest biological action, prevents penetration of UVB radiation, avoiding radiation effects on cells, including immunosuppression (Costa 2012; Bagatin 2009). The studies show that topical application of green tea polyphenols, in concentrations of 1–10%, reduces the erythema induced by UV radiation, the number of sunburn cells, and DNA damage (Bagatin 2009). It can also be administered orally in combination to other substances (Florez-White 2013; Bagatin 2009).
- Silimarin: A bioflavonoid component of the *Silybum marianum* fruit, of phenolic nature, capable of reacting with numerous free radicals to form more stable and less reactive compounds (Florez-White 2013). Topical applications have shown photoprotective effects when used before or after irradiation (Costa 2012). More recently, good results have been observed when used as an adjunct in the treatment of telangiectasic rosacea (Florez-White 2013; Berardesca et al. 2008).
- *Coffea arabica:* extracted from coffee plant fruit, known for its powerful polyphenols with powerful antioxidant activity (Costa 2012). Studies show that 1% topical application improves hyperpigmentation, fine lines, and wrinkles after 6 weeks of use (Costa 2012).
- Resveratrol: polyphenolic compound found in grapes, nuts, fruit, and red wine (Costa 2012). It is a potent antioxidant with anti-inflammatory and anti-proliferative effects, and its topical application appears to protect against damage and UVB-mediated oxidative stress (Bagatin 2009).
- Pomegranate: the extract can be obtained from *Punica granatum* fruit, juice, and rind, and its phenolic compounds have powerful antioxidant activity (Costa 2012). It has been shown in vivo that topical application of bark extract restored the activity of catalase, peroxidase, and superoxide dismutase (Florez-White 2013). The fruit extract in vitro improved cell-mediated damage by UVA and UVB (Costa 2012).
- Genistein: An isoflavone derived from soybeans that are capable of inhibiting oxidative DNA damage caused by ultraviolet radiation (Florez-White 2013; Bagatin 2009). It can be administered topically or orally (Costa 2012).
- *Polypodium leucotomos:* obtained from fern species, rich in phenolic compounds with antioxidant and photoprotective activity (Costa 2012). In vitro and in vivo studies demonstrated significant reduction in the number of sunburn cells, cyclobutane pyrimidine dimers, and epidermal cell proliferation after UV radiation (Florez-White 2013; Costa 2012). It is used as an oral sunscreen, with special interest in patients with photosensitive skin diseases (Nestor et al. 2014). It is also observed additional benefit when used as an adjunct in the treatment of pigmentation disorders such as vitiligo, melasma, and postinflammatory hyperpigmentation (Nestor et al. 2014).

Other Antioxidants

- Pycnogenol: extracted from the bark of the French maritime pine (*Pinus pinaster ssp atlantica*) is a concentration of phenolic compounds and flavonoids with high capacity for scavenging free radicals by intramolecular

rearrangements (Costa 2012). It assists in the treatment of melasma and prevention of skin damage induced by UV radiation, with a significant reduction in the formation of erythema (Florez-White 2013). Studies have shown increased minimal erythema dose and reduced hyperpigmentation with oral supplementation of Pycnogenol (Costa 2012).

- Niacinamide (nicotinamide): biologically active analog of vitamin B3, which has antioxidant, anti-inflammatory, immunomodulatory, and depigmentation activity (Costa 2012; Kawada et al. 2008). It is thought to improve the texture and skin tone, reduces fine lines, wrinkles, and hyperpigmentation (Kawada et al. 2008).

Hydroxy Acids: Alpha Hydroxy Acids, Beta Hydroxyl Acids, Poly Hydroxy Acids, and Bionic Acids

Initially described for the treatment of dermatosis associated with hyperkeratosis, hydroxy acids are now widely used for cosmetic purposes, because they promote and improve the appearance of photoaged skin texture (Costa 2012).

Hydroxy acids are chemically classified as organic carboxylic acids, since they contain in their composition carbon and hydrogen molecules (Costa 2012). They are capable of increasing the synthesis of extracellular matrix components in the dermis, increasing the thickness and firmness of the skin, aside from promoting thinning of the stratum corneum and cell renewal, with an improvement also observed in hyperpigmentation (Kawada et al. 2008). They can be used in daily topical treatment or high concentrations peels (Florez-White 2013). Combined with different actives, they show additional or synergistic effects, thus optimizing the response to, for example, the use of retinoids and depigmenting agents (Costa 2012). Didactically they are divided into alpha hydroxy acids, beta hydroxy acids, poly hydroxy acids, and bionic acids (Costa 2012).

Alpha Hydroxy Acids (AHA)

These substances are organic carboxylic acids with a hydroxyl group (-OH) attached to the α position of the carboxyl grouping (Costa 2012; Barquet et al. 2006). They are found in foods and fruits as well as metabolites of the pathway of carbohydrates (Florez-White 2013; Barquet et al. 2006). In its free form, they have a higher bioavailability compared to their salts, which are almost completely dissociated and are not so easily able to penetrate the stratum corneum of intact skin (Costa 2012). They also act as antioxidants, with the ability to neutralize or prevent the production of free radicals (Costa 2012).

Histologically, intercorneocites decrease the cohesion in the deeper layers of the stratum corneum resulting in the temporary thinning of that layer, which results in clinically soft, smooth, and flexible skin with less tendency to wrinkle (Costa 2012). These substances regulate the effects on the keratinocyte differentiation and keratinization (Barquet et al. 2006). In the dermis, they increase the synthesis of collagen, decrease the degradation of the elastic fibers, and increase the deposition of glycosaminoglycans in the extracellular matrix, what improve elasticity, tone, and appearance of wrinkles (Costa 2012).

The pH of AHA formulation is important in determining its efficacy (Costa 2012; Barquet et al. 2006). Typically such compositions are acidic, with a pH less than 3.0, in the absence of neutralization (with an organic base or inorganic alkali) (Costa 2012). The lower the pH, the greater the irritation, erythema, burning sensation, and the likelihood of irregular penetration leaving areas of greater depth (Costa 2012). To overcome this issue, a buffer should be used with partial neutralization of the solution, improving tolerability without compromising effectiveness (Barquet et al. 2006).

- Glycolic acid (GA): is present in sugar cane (Barquet et al. 2006). It is the most widely used AHA because it has a smaller molecule and more rapid skin penetration in comparison with other assets (Costa 2012). Due to easy absorption, it commonly causes irritation with redness, itching, and burning (Florez-White 2013). It is very soluble in water and has different pH's in aqueous solutions depending on the concentration (Costa

2012). A buffering formula is frequently used to decrease irritative potential (Florez-White 2013). Another described adverse effect is post-inflammatory hyperpigmentation, especially in individuals of darker skin (Costa 2012; Barquet et al. 2006). The GA promotes dissolution of comedones, as well as, prevents their formation by decreasing the adhesion of corneocytes and the follicular epidermolysis effect (Florez-White 2013). It is very useful in the treatment of inflammatory lesions of acne and rosacea and additionally improves clinical signs resulted from photoaging (Costa 2012).

- Lactic acid: is the second smallest AHA, found in milk and tomatoes (Florez-White 2013). It is the weakest epidermolytic compared to GA, causing less irritation (Costa 2012). It is widely used in xerotic processes due to their keratolytic and antiproliferative effect in a 2–5% concentration (Barquet et al. 2006). The ammonium lactate (used at a concentration of 14%) is a derivative of lactic acid salt with high humectant power, capable of cell renewal and increase in the amount of glycosaminoglycans (Costa 2012).
- Malic acid: found in grapes, oranges, and apples. It provides long-lasting hydration and softness to skin (Florez-White 2013; Costa 2012).
- Tartaric acid: found in grapes with significant antioxidant action (Costa 2012).
- Citric acid: found naturally in citrus fruits, has antiaging benefits equivalent to GA and the ability to stimulate collagen synthesis (Costa 2012).
- Mandelic acid: obtained from the hydrolysis of bitter almond extract. It is the AHA with the biggest molecular weight, which leads to slower penetration and low irritation potential; therefore, mandelic acid is safer for use with darker skin tones (Costa 2012). It is used to treat acne because of its antiseptic and anti-inflammatory properties and also promotes significant improvement in hyperpigmentation (Barquet et al. 2006).
- Pyruvic acid: the skin is converted into lactic acid by the action of the lactate dehydrogenase enzyme (Florez-White 2013). It penetrates through the lipophilic skin and sebaceous glands; therefore, it is indicated to treat oily skin (Florez-White 2013).
- Protacid®: it is glycolic acid connected to soy protein (Costa 2012). The advantage of its use is the possibility of keeping the keratolytic action of GA in a pH more compatible to the skin, reducing irritation and increasing tolerance (Costa 2012).
- Mixed fruit acid complex (MFA Complex®): It is a compound formed by the association of lactic, citric, and malic acid to green tea in order to reduce the irritating effects of the AHA (Costa 2012). It has moisturizing, antiaging, and regenerative actions; it promotes exfoliation (Costa 2012).

Beta Hydroxy Acids (BHA)

BHA are organic carboxylic acids which have a hydroxyl on the β position of the carboxyl grouping (Costa 2012). They can be found in the organism as intermediary metabolites and sources of energy (Costa 2012). Some molecules are, at the same time, AHA and BHA, as they contain one hydroxy group in α position of one carboxyl grouping and another in β position to any other group, for example, malic acid (Florez-White 2013; Barquet et al. 2006).

- Salicylic acid (SA): It is a BHA not soluble in water (Florez-White 2013). At concentrations below 3%, it acts as a keratoplast, improving the appearance of photodamaged skin (Costa 2012). At concentrations of 3–5%, it is keratolytic and facilitates the penetration of other topical agents (Florez-White 2013). It can be used in peeling at concentrations of 10–30% (Costa 2012). It is very useful in the treatment of acne, for its antiseptic action and high lipophilic penetration through the skin and sebaceous glands (Costa 2012). It is also used to treat psoriasis, keratosis pilaris, and warts; it may be combined with other agents, such as corticosteroids and lactic acid (Florez-White 2013; Costa 2012). It should not be applied on large areas for prolonged periods or at risk

of systemic toxicity, which occurs when the serum salicylate levels reach 200–400 mg/ml, although this effect is unlikely to occur with topical use (Costa 2012).

Poly Hydroxy Acids (PHA)

PHA are organic carboxylic acids with two or more hydroxyl groups bonded to carbon atoms of an aliphatic or alicyclic chain (Costa 2012). Multiple hydroxyl groups addition to the HA molecule increases water binding capacity and water retention, contributing to higher moisturizing effect compared to AHA (Florez-White 2013). They are found in nature as endogenous metabolites or as intermediate products of carbohydrate metabolism in tissues (Florez-White 2013; Barquet et al. 2006).

- Gluconolactone (GL): It has keratolytic, moisturizing, antioxidant, and antiaging properties (Costa 2012; Barquet et al. 2006). Thanks to its lactonic structure, this agent hides its acidic nature, being tolerated even by sensitive skin and areas such as eyes and lips (Costa 2012). In vitro studies have demonstrated protection against UV radiation (Florez-White 2013). It is used at a concentration of 4–10% and can be formulated with other substances (Costa 2012). It optimizes the effects of retinoic acid and minimizes the irritation caused by benzoyl peroxide (Florez-White 2013; Barquet et al. 2006).

Bionic Acids

They consist of a carbohydrate monomer linked to one PHA-aldonic acid (Costa 2012). The molecules are larger than the traditional AHA but small enough to slowly penetrate skin (Costa 2012). One of the biggest benefits is its low irritation action (Costa 2012).

- Lactobionic Acid (LA): It is the most used bionic acid in cosmeceutical products. It is characterized by the connection of gluconic acid molecule with a D-galactose molecule, a sugar required for synthesis of glycosaminoglycans (Costa 2012). It has high hygroscopicity, forming a gel matrix when the aqueous solution evaporates at room temperature (Florez-White 2013; Costa 2012). Formulations with LA are very well tolerated, even on sensitive skin, and are also indicated after procedures like peels and dermabrasion, because of its protective effect and soothing (Florez-White 2013).

Retinoid Cosmetics

Retinoids (RET) – natural or synthetic vitamin A (retinol) derivatives – play a crucial role in regulating growth and epidermal differentiation on the skin (Costa 2012).

All RET are made by one ß-ionic ring ligated to a polyunsaturated chain with alcohol, aldehyde, carboxylic acid, or ester group (Afornali et al. 2013). Biologically they exert their effect by binding to specific nuclear receptors, either RAR (retinoic acid receptors) or RXR (retinoid X receptors), interacting with DNA sequences located in the promoter regions of specific genes (Costa 2012). Such sequences are known as response elements to retinoic acid (RARE) (Costa 2012). There are two major families of retinoid: acids and nonacids (Costa 2012) (Table 2).

Table 2 Retinoid classification according to its acidity

Acids	*Isotretinoin* 0.05% in gel
	Tretinoin 0.025%, 0.05%, 0.1% and 0.4% in cream 0.01%, 0.025% and 0.05% in gel 0.05%, 0.1% and 0.2% in solution 0.1% in lotion 0.05% in oil 0.05% in packs
Nonacid	*Retinyl palmitate* 0.5% to 5% in lotion and cream
	Retinyl acetate
	Retinal (retinaldehyde) 0.05% in cream, gel, and lotion
	Retinol 0.01% to 0.4% in cream
	Adapalene 0.1% and 0.3% in gel
	Tazarotene 0.05% and 0.1% in gel

The acid forms act preferentially on RAR-type receptors, whereas RXRs are more activated by nonacidic forms (Costa 2012). However, the biological effects are very similar regardless of the activated receptor and include improvement of fine wrinkles, dermal striae, actinic keratosis, and acne vulgaris, as well as decreasing roughness and reducing hyperpigmentation (Costa 2012; Afornali et al. 2013). Histologically, it is possible to be found epidermal hyperplasia, compaction of the stratum corneum, granular layer and melanocytic hypertrophy reduction, restoration of cell porosity, increased angiogenesis, neocollagenesis, and normalization of skin elasticity (Costa 2012).

From now, we are going to explore some specificity observed with each RET agents:

- Retinyl palmitate: It is the retinol ester that represents the main vitamin A form reached on skin (Oliveira et al. 2014). Despite of penetrating the skin only slightly, retinyl palmitate can be converted into retinol, and so presents softer and less irritating cosmetic profile (Costa 2012; Oliveira et al. 2014).
- Retinol: It is vitamin A in its free form, nonesterified, and extremely oxidant in light and heat (Costa 2012).
- Retinaldehyde: Is an intermediate precursor of tretinoin with less efficacy but less irritating effect as well (Costa 2012).
- Tretinoin (retinoic acid): It is considered the gold standard in the topical approach of photoaging, once it accelerates cellular turnover, stimulates neocollagenesis, and provides dermal neovascularization (Costa 2012; Mukherjee et al. 2006). Clinically, it is noticed that, after 3 months of use, the stratum corneum is thinned, compact, with a double thick epidermis and a more regular growth pattern, with the disappearance of nuclear atypia and keratoses; in the fourth month of use it is observed thickening and regularization of Grenz zone (rich in type IV collagen), projecting into the papillary dermis, with regeneration of blood capillaries (Costa 2012). It is believed that this neocollagenesis remains intact until the fourth months after the date of the last use of tretinoin (Costa 2012). Burning, redness, peeling, and xerosis occur in 70–90% of users, and those symptoms are considered limiting factors for its continued and uninterrupted use (Costa 2012).
- Isotretinoin (9-cis retinoic acid and 13-cis retinoic acid): used for the treatment of acne vulgaris by decreasing sebaceous gland activity and the propagation of *Propionibacterium acnes* (Mukherjee et al. 2006). It is a more tolerable alternative to tretinoin in photoaging approach; it also stimulates neocollagenesis and inhibits metalloproteinase action (Costa 2012).
- Adapalene: indicated in cases of mild to moderate acne, has anti-inflammatory, antiproliferative, and comedolytic actions (Florez-White 2013; Mukherjee et al. 2006). Studies show that can also be used in topical approach of photoaging (Costa 2012).
- Tazarotene: has anti-inflammatory, antiproliferative, and normalizes the differentiation of keratinocytes (Costa 2012). Initially, it was used for the topical treatment of plaque psoriasis and acne vulgaris; increasingly, it has shown great use in photoaging treatment because it reduces the roughness, mottled pigmentation, and the appearance of fine wrinkles (Florez-White 2013). However, it has high irritant potential (Costa 2012; Mukherjee et al. 2006).

Peptides

Protein-based substances have a beneficial effect on the skin by inducing collagen synthesis and stimulating angiogenesis. Amino acids may also be useful in the processes related to inflammation, pigmentation, cell proliferation/migration, immunity, and extracellular matrix synthesis (Bruce 2008; Chung et al. 2004; Daithankar et al. 2005; Gorouhi and Maibach 2009; Lupus and Cole 2005, 2007; Lupus 2005). Such indications predicted the topical use of these products (Gorouhi and Maibach 2009). However, to properly reach those effects, such molecules need to penetrate into the action site in an active mode, exercising their function without causing

hypersensitivity (Lupus 2005). Many molecules are rapidly degraded and others are hydrophilic and can not cross the lipophilic skin barrier (Bruce 2008; Chung et al. 2004; Daithankar et al. 2005; Gorouhi and Maibach 2009; Lupus and Cole 2005, 2007; Lupus 2005).

The permeation capability of a product depends on its pH, molecular weight, chemical stability, binding ability, and solubility (Lupus and Cole 2007). Further, the integrity of the skin as well as its thickness, local metabolism and frequency of application, the vehicles used, and the available time for use before degradation are all considered equally important conditions to allow product penetration (Bruce 2008). A change in physicochemical structure of the peptides to increase its permeability and maintain stability is fundamental for their action (Chung et al. 2004). These products improve the texture, turgor, and the regularity of the surface without the undesirable effects that retinoids cause (Afornali et al. 2013; Oliveira et al. 2014; Mukherjee et al. 2006; Bruce 2008; Chung et al. 2004; Daithankar et al. 2005; Gorouhi and Maibach 2009). These substances, on a molecular and functional level, are able to increase collagen regeneration and prevent its degradation (Afornali et al. 2013; Oliveira et al. 2014; Mukherjee et al. 2006; Bruce 2008; Chung et al. 2004; Daithankar et al. 2005; Gorouhi and Maibach 2009). They are classified into flags, neurotransmitter inhibitors, transporters, and enzymes inhibitors (Afornali et al. 2013; Oliveira et al. 2014; Mukherjee et al. 2006; Bruce 2008; Chung et al. 2004; Daithankar et al. 2005; Gorouhi and Maibach 2009).

The signal peptides stimulate fibroblasts, increase collagen and elastin production, reducing the action of collagenase (Bruce 2008; Chung et al. 2004). Also, they increase the amount of glycosaminoglycans, proteoglycans, and fibronectin, leading to a final result of healthy skin with decreased lines and wrinkles caused by aging, making the skin firmer and more youthful (Bruce 2008; Chung et al. 2004). One of the best-known active ingredients is Matrixyl® and can be incorporated into various formulations (Daithankar et al. 2005). Another active ingredient is biopeptide-CL®, which operates an aminoacid sequence that stimulates fibroblast activation (Daithankar et al. 2005). The lipospondim® and SYR-coll® are also functional peptides that promote correction of wrinkles and moisturizing the skin surface (Daithankar et al. 2005).

Different types of botulinum toxin represent neurotransmitters inhibitory peptides and act in muscle movement (Gorouhi and Maibach 2009; Lupus and Cole 2005, 2007; Lupus 2005). Some topic cosmeceuticals can bind to the neurotransmitter membrane also reducing muscle mobility. These principles are the Argireline®, Vialox®, Leuphasyl®, and Syn® -lke (Gorouhi and Maibach 2009; Lupus and Cole 2005, 2007; Lupus 2005).

Transport peptides are capable of stabilizing carriers and enable the transfer of metals such as copper (Gorouhi and Maibach 2009). Copper acts as a cofactor of SOD, since it catalyzes the dismutation of superoxide into oxygen and hydrogen peroxide (Lupus 2005; Mazurowska and Mojski 2008; Namjoshi and Benson 2010; Rivers 2008).

Enzyme inhibitory peptides inhibit the action of proteases, such as metalloproteinase and tyrosinase (Mukherjee et al. 2006; Bruce 2008; Chung et al. 2004; Daithankar et al. 2005; Gorouhi and Maibach 2009; Lupus and Cole 2005, 2007; Lupus 2005). They are often used in anti-aging creams, moisturizers, sunscreens, and hair care products. They may be derived from soybeans, rice, and silk protein (Lupus 2005).

Some specific growth factors are connected to peptides, concentrating their actions in specific organs; for this reason, they can be used in cosmesceutical products (Daithankar et al. 2005).

With a lot of attention in the media, peptides with "Cinderella" effects are high molecular weight proteins with a filmogenous characteristic, which means, as it dries, there is a shrinkage of the film layer over the skin, making the surface smooth and less tense (Daithankar et al. 2005; Gorouhi and Maibach 2009; Lupus and Cole 2005, 2007; Lupus 2005; Mazurowska and Mojski 2008; Namjoshi and Benson 2010; Rivers 2008). They are branded as Tensine®, Raffermine®, Easelift®, Liftline®, Pepha-TAGHT®, and Cesaflash®. The peptides are

generally well tolerated with little risk of adverse reaction.

Miotensors, Muscle Relaxants, and Dermal Fillers

Lax skin occurs due to evolutionary changes of the connective tissue structure – represented by the extracellular matrix with its collagen, elastic, and reticular fibers – that provides tone and elasticity to the skin (Costa 2012). In addition to the damage to the connective tissue, it is also added the gravitational effect and the mobilization of the subcutaneous tissue, and most recently seen, the interference of the dynamic changes produced by hypertension of facial movements and their repeated contractions, or, by muscle hypotonia in the aging process (Costa 2012). Cosmeceuticals with muscle contracting activity or muscle relaxant one are assets that could modulate skin tension; however, this concept remains controversial, since to exercise muscle activity, the assets should exceed the entire skin barrier (Costa 2012).

Compounds with Immediate Tensor Action

These are vegetable origin agents that produce immediate tightening effect on the skin by forming a film on the skin surface, the so-called "Cinderella Effect" (Costa 2012). To remain on the skin and act as filmogenic, the proteins must have a high molecular weight between 20,000 and 150,000 daltons (Florez-White 2013). Coming up, some immediate tensor action compounds are described:

- Wheat seed proteins (Tensine®): extract of wheat seed protein (*Triticum sp*), this cosmetic asset forms a film on the skin, making it firmer and reducing the depth of wrinkles (Costa 2012). The effect occurs one hour after application and persists for approximately 6 h. They can be manipulated at a concentration of 3–10% (Costa 2012).
- Wheat proteins (Liftline®): Special fractions obtained from wheat protein form an elastic, durable, and continuous film on the surface of the skin, improving softness and firmness, apart from reducing flacid skin and fine lines (Costa 2012). Used at a concentration of 3–5% (Costa 2012).
- *Pisum sativum* protein (Vegetensor®): protein association of *Pisum sativum*, rich in essential aminoacids, and natural polysaccharide *Sclerotium gum,* with tension of immediate effect. Used in concentrations of 1–5% (Costa 2012).
- Polysaccharide and gum acacia (Easylift®): compound of immediate tightening effect, which can be incorporated into any type of formulation at a concentration of 1–3% (Costa 2012; Wagas et al. 2015).

Skin Firming Substances

- Hydrolyzed soy extract (Raffermine®): dermal firming agent, hydrolyzed soy (*Glycine soya*) which contains glycoproteins and polysaccharides (Costa 2012). Its biomimetic action to dermal glycoproteins enables the skin substance to regulate interactions between dermal components, and, in particular, facilitates the connection of fibroblasts to collagen fibers (Wagas et al. 2015). It has an inhibitory effect on elastase, while preserving skin elasticity and directly stimulating the contraction of fibroblasts, enhancing the molecular structure of the dermis, increasing the firmness, elasticity, and skin tone (Costa 2012). Used at a concentration of 2–5% (Costa 2012; Wagas et al. 2015).
- L-fucose and L-rhamnose (Elastinol + R®): combination of polysaccharides rich in L-fucose and L-rhamnose that act in the dermis and epidermis, stimulating cell proliferation and synthesis of molecules of the extracellular matrix. Used at a concentration of 1–5%.
- Deanol® or 2-dimethylaminoethanol (DMAE): a vitamin B choline analog tertiary-amine and acetylcholine precursor, an important neurotransmitter involved in the process of muscle contraction (Costa 2012).

The exact mechanisms by which DMAE is suggested to produce a firming effect on the skin

are not fully understood; it is postulated that this substance could enhance the synthesis of acetylcholine at the neuromuscular junction, modulate muscle contraction by increasing the contractile force, which could explain the feeling of skin tightness (lifting effect) (Costa 2012; Liu et al. 2014). The topical application of 3% DMAE gel reduces fine lines and wrinkles and increases skin firmness (Costa 2012). Another important aspect is the fact that DMAE, by increasing the release of acetylcholine in pre-synaptic cleft, has the opposite effect to that of botulinum toxin, which prevents the release of that neurotransmitter; however, it is not uncommon to observe the concomitant use of such substances (Mazurowska and Mojski 2008).

Another mechanism of action would be the stabilization of the cell membrane (the formation of phosphatidylcholine), which would result in anti-inflammatory and antioxidant effect (Wagas et al. 2015). It notes that excessive concentrations of DMAE, in vitro, can cause backfire, as it seeks to facilitate neurotransmission and not neuromuscular blockade, which would cause paralysis of the contractile response (Mazurowska and Mojski 2008).

- Pro-Xylane®: Molecule obtained from xylose, natural sugar from beech tree, cultivated in Western Europe, with the in vitro ability to start glycosaminoglycans synthesis in the dermis and epidermis, and they make it possible to fix the protein carrier to form proteoglycans (Costa 2012). It stimulates the synthesis of collagen IV and VII, laminin 5, tenascin C, and fibrillin 1, increasing dermal-epidermal cohesion. It improves wrinkles and flacid skin after 3 months of use, and the increased tone can already be observed after 1 h of application of Pro-Xylane® 5% (Costa 2012).
- Tetra-hydroxypropyl ethylenediamine (THPE®): It is supposed to modulate the contraction of superficial epidermal keratinocytes, improving facial contour, the appearance of dark circles, fine lines, and wrinkles of the periorbital region after a few minutes of topical application and may keep a tightening effect for a few hours (Costa 2012).
- Natural secretion of *Cryptomphalus aspersa*® (SCA®): mucoid substance obtained from natural secretion *Cryptomphalus aspersa* mollusc, with antioxidant effects and the ability to stimulate the proliferation of fibroblasts, fibronectin production, actin cytoskeletal rearrangement of the extracellular matrix, and regulation of activity of matrix metalloproteinases (MMP) (Costa 2012).

Muscle Relaxants

- Argireline®: in vitro, inhibits the release of neurotransmitters by interfering with the formation and stabilization of the protein complex necessary for the release of acetylcholine at the neuromuscular junction, raising the threshold for minimum muscle activity (Costa 2012). This results in the need for more stimulus for the muscle to contraction (Grosicki et al. 2014). It reduces the depth of fine lines and facial wrinkles (Costa 2012).
- Topical botulinum toxin: more recently, it has been demonstrated the effectiveness of topical application of botulinum toxin formulated in nanotechnology vehicles for cosmetic treatment of wrinkles and hyperhidrosis (Atomoros 2009). Studies have shown that the toxin is stable at room temperature and can be measured by the amount of cream applied, penetrating skin without damaging its cutaneous integrity and with no evidence of systemic toxicity or spread beyond the targeted muscle (Costa 2012). More studies, however, are needed to optimize and standardize the topical use of such asset.

Volume Enahncers and Dermal Fillers

These are substances capable of penetrating the skin surface and modifying the treated skin, by improving aspects related to aging such as wrinkles, loss of elasticity, dryness, and textural changes. They create and provide a volumizing filler effect, therefore are of easy access and use; have low cost, become very popular substances and are widely accepted among patients (Costa 2012).

Table 3 summarizes the most important compounds that are under this class of cosmeceuticals.

Table 3 Active cosmeceuticals with effects of volume enhancers and dermal fillers

Cosmeceutical	Action mechanism	Origin
Anthraquinone	Stimulates the biosynthesis of collagen type I and glycosaminoglycans Reduces MMP-1 expression	*Morinda citrifolia* fruit extract
Extract form the inner chestnut layer	Increases fibronectin and vitronectin expression	*Castanea crenata S. et Z. Fafaceae*
Growth factors	Stimulate the synthesis of growth factors from keratinocytes, which activate dermal fibroblasts leading to remodeling and regeneration of the dermal extracellular matrix	Recombinant Fibroblasts Keratinocytes
Hyaluronic acid	Emollient and moist	Recombinant Fibroblasts
Asiaticoside	Increases collagen type I synthesis Stimulates fibroblast proliferation Increases extracellular matrix synthesis	*Centella asiatica*
Dimethylaminoethanol (DMAE)	Increases filaggrin Stimulation of acetylcholine	Anchovies, sardines, and salmon
Coenzime Q10 (ubiquinone)	Increases glycosaminoglycans levels Increases cell production Slows down hyaluronic acid loss	Living cells (except bacteria and fungus)
Commipheroline®	Favors lipogenesis Limits lipolysis	*Commiphora mukul*
Tetra-hydroxy-propyl-ethylenediamine (THPE®)	Contracts keratinocytes	Biotechnology
Hibiscus extract rich in amino acids (Linefactor®)	Acts on FGF-β or FGF-2 Stimulates the synthesis of collagen and glycosaminoglycans	*Hibiscus abelmoschus* seed

Growth Factors

Hundreds of growth factors have been identified and taken place as important agents in the skin healing process (Babu and Wells 2001; Broughton et al. 2006). Some of them are involved in the immune response, as well as the synthesis of collagen, elastin, and glycosaminoglycans (GAC), all of them are considered components of the dermal extracellular matrix that are affected by UV radiation (Babu and Wells 2001; Broughton et al. 2006).

Some of the biochemical effects of skin aging are similar to the healing of a wound (Eming et al. 2007). Both the formation of a wound and the secondary cell damage from UV radiation induce the activation of inflammatory pathways (Babu and Wells 2001). Inflammation produces free radicals and proteolytic enzymes, resulting in harmful effects to the extracellular matrix (Broughton et al. 2006). Successful healing demands balance between the development of inflammation and rapid resolution. The intrinsic aging does not show a major inflammatory component as observed in wound healing but generates mitochondrial oxidative stress that produces some of the major mediators involved in degradation of extracellular matrix, including free radicals (Bagatin 2009; Broughton et al. 2006).

The use of growth factors (TGF-beta, EGF, PDGF, and others) and cytokine in rejuvenation is being studied in the treatment of photoaging (Eming et al. 2007; Fitzpatrick and Rostan 2003; Hilling 2010; Mehta and Fitzpatrick 2007). It has been shown new collagen formation, epidermal thickening, reducing perioperative orbital wrinkles, and improved texture under their use (Fitzpatrick and Rostan 2003).

The growth factors can be used as adjuvants in the procedures of ablative or nonablative lasers (Eming et al. 2007; Fitzpatrick and Rostan 2003; Hilling 2010; Mehta and Fitzpatrick 2007). The laser resurfacing alters the barrier properties allowing greater penetration of the growth factors, as their combination can improve the recovery or obtain a synergistic effect (Eming et al. 2007;

Fitzpatrick and Rostan 2003; Hilling 2010; Mehta and Fitzpatrick 2007). Growth factors can penetrate the skin through hair follicles, sweat glands, or compromised skin, such as dermal abrasions and xerosis (Eming et al. 2007).

The lipophilic penetration promoters or barrier peptide modifiers can enhance the penetration of these proteins through intact skin (Grosicki et al. 2014; Júnior et al. 2007; Babu and Wells 2001; Broughton et al. 2006; Eming et al. 2007; Fitzpatrick and Rostan 2003; Hilling 2010). There are no proven risks associated with topical application of growth factors except for sensitivity reaction to these substances (Grosicki et al. 2014; Júnior et al. 2007; Babu and Wells 2001; Broughton et al. 2006; Eming et al. 2007; Fitzpatrick and Rostan 2003; Hilling 2010). It is unlikely that topical application of growth factors, such as VEGF, leads to tumor growth; however, no data is provided whether they can stimulate or not the hypertrophic scars (Broughton et al. 2006).

Topical Enzymes

Enzymes are highly specific and are considered complex catalyst proteins that increase the rate of chemical and cellular reactions (Mehta and Fitzpatrick 2007; Chung et al. 2001; Darby and Hewitson 2007; El-Domyati et al. 2002; Brooks et al. 1997; Draelos et al. 2009; Lods et al. 2000). Application of these enzymes has been utilized in cosmeceutical industry for skin rejuvenation and protection (Brooks et al. 1997; Draelos et al. 2009).

The oxidoreductases are part of an antioxidant defense system that eliminates free radicals, neutralizing harmful substances and pollution generated by solar exposure (Lods et al. 2000). The excessive exposure to UV radiation can overcome the skin antioxidant capacity, leading to oxidative damage, that lead to immunosuppression, premature aging, and skin cancer (Brooks et al. 1997; Draelos et al. 2009; Lods et al. 2000).

To effectively combat environmental damage, administration of antioxidant enzymes, such as SOD, peroxidase, catalase, and glutathione peroxidase, support the endogenous antioxidant system (Lods et al. 2000). Supplementation of nonenzymatic antioxidants, such as glutathione, alpha-tocopherol, ascorbic acid, and beta-carotene, also confer increased effectiveness of protection against oxidative damage (Mehta and Fitzpatrick 2007; Chung et al. 2001). SOD is one of the most important enzymes in skin protection because it promotes the removal of oxygen radicals and inhibits lipid peroxidation (Lods et al. 2000). Superoxide radicals are toxic to cells because they damage the fatty acids of the lipid membrane, causing cell damage (Lods et al. 2000). Several studies show that topical administration of endogenous antioxidants are effective in protecting skin, and the SOD may be used in sunscreens to enhance their effectiveness (El-Domyati et al. 2002; Brooks et al. 1997).

Peroxidases are enzymes that oxidize organic substrates and have hydrogen peroxide as an electron capturing molecule in a reaction called peroxidation (Lods et al. 2000). The peroxidase system is a defense mechanism used to prevent bacterial growth (El-Domyati et al. 2002; Brooks et al. 1997; Lods et al. 2000). The catalase is an intracellular enzyme that also breaks down the hydrogen peroxide acting, therefore, as a peroxidase (El-Domyati et al. 2002; Brooks et al. 1997).

Proteases are able to cleave proteins (Lods et al. 2000). Studies show that the application of proteases in the skin leads to epidermal ablation and may act as chemical peels (Brooks et al. 1997; Draelos et al. 2009; Lods et al. 2000).

Bromelain is a crude extract from pineapples that has anti-inflammatory, fibrinolytic, platelet aggregation inhibition activities, and skin debridement properties, and it can be used in the clinical debridement of skin ulcers and scab removal (Costa 2012). The papain, a proteolytic enzyme extracted from papaya, is indicated for the treatment of wounds (Costa 2012). There are a group of enzymes that repair DNA that was damaged by UV radiation (Babu and Wells 2001; Broughton et al. 2006; Eming et al. 2007; Fitzpatrick and Rostan 2003; Hilling 2010; Mehta and Fitzpatrick 2007; Chung et al. 2001; Darby and Hewitson 2007; El-Domyati et al.

2002; Brooks et al. 1997; Draelos et al. 2009; Lods et al. 2000). These enzymes include T4endonuclase 5, photolyase, and 8 oxoguanine 1 glycosylase (Babu and Wells 2001; Broughton et al. 2006; Eming et al. 2007; Fitzpatrick and Rostan 2003; Hilling 2010; Mehta and Fitzpatrick 2007; Chung et al. 2001; Darby and Hewitson 2007; El-Domyati et al. 2002; Brooks et al. 1997; Draelos et al. 2009; Lods et al. 2000).

The intrinsic aging process involves the action of telomerases (Brooks et al. 1997; Rona et al. 2004; Steenvoorden and van Henegouwen 1997). Telomeres are protective structures presented at the ends of chromosomes and at each cell replication have a progressive shortening (Rona et al. 2004). When they reach a critical shortening point, cell growth is stopped and culminates in senescence and cell death (Rona et al. 2004; Steenvoorden and van Henegouwen 1997). Telomeres are also called biological clocks and their length is inversely proportional to age (Brooks et al. 1997; Rona et al. 2004). The enzyme telomerase, a special type of reverse trascriptase, is capable of replicating the telomeres of stem cells and embryonic stem cells (Rona et al. 2004). Till the present moment, there are insufficient data to demonstrate the safety of using telomerase (Rona et al. 2004).

Glycan Inhibitors

The enzymatic glycosylation process is well studied in diabetic patients and shows that the glucose degradation products react with various molecules, such as collagen and other proteins, to form irreversible structures, called glycation end products (AGE) (Barbosa et al. 2008). These lead to malfunctions and damages of various organs, as well as skin aging (Barbosa et al. 2008; Dandy and William 2010).

AGEs damage the skin through three mechanisms: (1) modification of intracellular structures involved in gene transcription; (2) protein interaction with the extracellular matrix that alter signaling molecules; and (3) protein and serum lipid modification which bind to specific receptors and lead to the release of inflammatory cytokines and growth factors (Barbosa et al. 2008; Dandy and William 2010; Daniel et al. 2002; Dryer et al. 1993).

The endogenous pool of AGE depends on exogenous glucose consumption, their elimination, and their endogenous formation (Barbosa et al. 2008). Genetic factors are also added in AGEs metabolism and consequently the development of diseases such as diabetes, atherosclerosis, arthritis, osteoporosis, and Alzheimer's disease (Barbosa et al. 2008; Dandy and William 2010).

The factors that lead to skin aging are classified into intrinsic and extrinsic (Barbosa et al. 2008; Dandy and William 2010; Daniel et al. 2002). The extrinsic are related to environmental factors such as exposure to ultraviolet radiation, pollution, and smoking, among others (Daniel et al. 2002). As for the intrinsic factors, these are related to finite life of fibroblasts and the damage caused by free radicals, which accumulate throughout life (Barbosa et al. 2008; Dandy and William 2010; Daniel et al. 2002). The theory of Maillard glycation is considered one of the main factors involved in the aging process (Dryer et al. 1993).

The accumulation of AGE in the skin occurs primarily in collagen fibers and the structural changes that are caused alter the biomechanical properties of the skin (Ulrich and Cerami 2001). AGE can increase cellular oxidative stress and promote inflammatory reactions (Barbosa et al. 2008). Tobacco is an important source of toxic products of glycation and is considered an important exogenous source of AGE (Barbosa et al. 2008; Dryer et al. 1993). Some molecules from glycation lead to the formation of free radicals which bind lipoprotein membranes (Barbosa et al. 2008). Therefore, there is lipoprotein glycol-oxidation that affects the structure of the membrane (Barbosa et al. 2008; Dandy and William 2010).

Diabetes, from a dermatological approach, must be dealt with anti-AGE therapy to reduce side effects of glycosylation, which such patients are subjected to (Barbosa et al. 2008). There are several studies for developing agents such as medications, dietary supplements, and systemic

therapy with anti-AGE properties (Ulrich and Cerami 2001).

Good nutrition is a foundation of good health (Nestor et al. 2014; Ulrich and Cerami 2001). Under such statement, it is good to consider that carbohydrates should preferably have low-glycemic index (Barbosa et al. 2008; Dandy and William 2010; Daniel et al. 2002). In addition to the end products from glycation, high blood sugar levels release pro-inflammatory cytokines (Barbosa et al. 2008; Dandy and William 2010; Daniel et al. 2002). Damage related to inflammation and excessive sugar levels leads to an anti-inflammatory diet, which excludes trans-fatty acids, being rich in hypoglycemic foods, antioxidants and essential fatty acids, such as omega 3 (Barbosa et al. 2008; Dandy and William 2010; Daniel et al. 2002). This diet should also be rich in alpha-lipoic acid, vitamin E, vitamin C and its esters, and coenzyme Q10 (Barbosa et al. 2008; Dandy and William 2010; Daniel et al. 2002).

For topical use there are new cosmeceutical agents that act directly on the AGE damaged skin and antioxidants (Daniel et al. 2002; Dryer et al. 1993; Ulrich and Cerami 2001). Some of the cosmeceutical compounds with antiglicant action are aldenine, algisium C, alistin, ameliox, coffeskin, dragosine, trylagem, and preventhelia (Daniel et al. 2002; Dryer et al. 1993; Ulrich and Cerami 2001).

Fatty Acids

Fatty acids (FA) are carboxylic acids which have a carboxyl (-COOH) group attached to a saturated or unsaturated long chain alkyl group (Costa 2012). They are essential components of natural lipids and are present in cell membranes in larger amount in the brain, testis, and skin, particularly the stratum corneum (Costa 2012). The three main classes of membrane lipids are phospholipids, glycolipids, and cholesterol (Tanojo et al. 1998; Schmuth et al. 2005; Kim et al. 2010).

After dietary lipids, the second source of FA is the biosynthesis, which makes them to be produced from smaller molecules resulting from the catabolism of carbohydrates, aminoacids, and some other FA (Costa 2012). The FA are classified as saturated (SFA) and unsaturated fatty acids (UFA) and the latter are further divided into monounsaturated and polyunsaturated eicosanoids (Costa 2012; Tanojo et al. 1998). They can be found in products from plant and animal origin (Costa 2012; Tanojo et al. 1998). The polyunsaturated UFA are represented by the alpha-linolenic acid (ALA, or omega-3) and linoleic acid (LA, or omega-6) and are said essential fatty acids, once they cannot be synthesized by the organism, being acquired from the diet (Costa 2012; Tanojo et al. 1998; Kim et al. 2010).

The stratum corneum is formed by corneocytes and by a permeability barrier, formed by an extracellular lipid matrix, cornified envelope, and keratin fibrils aggregated by filaggrin (Schmuth et al. 2005). The extracellular lipid matrix is composed on average of 50% ceramides, 25–27% cholesterol, and 10–15% of free fatty acids (FFA), mainly palmitic and oleic, and the remainder of sulfate esters and cholesterol (Costa 2012; Schmuth et al. 2005). Ceramide is the basic molecule of the sphingolipid, formed by a long chain FA and an amide bond, being an essential component for the organization of lamellar barrier (Costa 2012). Cholesterol promotes the interconnection of different lipid species (Costa 2012; Schmuth et al. 2005). Epidermal FFA are predominantly saturated and have a very long chain (Schmuth et al. 2005). A decrease in the concentration of any of these lipid species affects the integrity of the barrier (Schmuth et al. 2005; Kim et al. 2010).

FA and Skin Barrier

The skin barrier function is mainly located in the stratum corneum and resides in the composition of this layer of lipids (sphingolipids, FFA, and cholesterol), which act as regulators of such property (Costa 2012; Tanojo et al. 1998). The FA can modulate the skin barrier (Costa 2012; Tanojo et al. 1998). Proof of this is that essential fatty acid–deficient individuals have defects in the permeability barrier with loss of integrity (Costa 2012; Tanojo et al. 1997). Increased transepidermal water loss, desquamation, and epidermal hyperplasia are essential FA deficit signs,

commonly observed with increasing age, whereas changes in the composition of lipids of the stratum corneum are inherent to the aging process (Tanojo et al. 1997). The topical application of products containing FFA improves skin barrier function, reducing scaling and epidermal hyperplasia (Tanojo et al. 1997).

FA and Skin Healing

The application of oily solution containing hyperoxygenated fatty acids (HFA), rich in essential fatty acids (60% LA), is effective for prevention and treatment of pressure ulcers at an early stage, aside from preventing venous stasis ulcers and promoting better tissue oxygenation (Costa 2012).

Essential FA and UV Radiation

Omega-3 can reduce radiation-induced skin acute inflammatory response by reducing the formation of pro-inflammatory cytokine, what makes dietary supplementation with omega-3 a safe option for additional protection against acute UV-mediated damage (Costa 2012; Rosenblat et al. 2011). A human skin ex vivo experiment demonstrated that polyhydroxylated fatty alcohols obtained from *Persia gratissima* (avocado) can provide sunscreen and anti-inflammatory effects (Rosenblat et al. 2011).

Essential FA and Atopic Dermitis

FA-based topical product prevents or alleviates eczema in patients with atopic dermatitis and is also useful in the acute phase of this disease because it seems to prevent the development of the initial inflammatory response mediated by Th-2 cells (Costa 2012; Billmann-Eberwein et al. 2002). It has also been shown to decrease the expression of the filaggrin gene in patients with atopic dermatitis, which contributes to the breakdown of the skin barrier, since the filaggrin is responsible for the aggregation of keratin filaments in the stratum corneum and facilitate the production of ceramides (Costa 2012; Billmann-Eberwein et al. 2002). Topical preparations containing ceramides, cholesterol, and free fatty acids are effective in the treatment of severe atopic lesions associated with increased dietary intake of beneficial FA, as LA and gamma-linolenic acid (Billmann-Eberwein et al. 2002).

Essential FA and Skin Cancer

Experimental studies in animals have shown that omega-3 are capable of inhibiting carcinogenesis induced by UV radiation, showing reduction in tumor proliferation, decrease of PGE-2 levels and inflammatory response, as well as significantly increasing the UV-mediated erythema threshold (Costa 2012; Rosenblat et al. 2011; Harris et al. 2005). In contrast, equivalent levels of omega-6 appear to increase the UV-mediated carcinogenesis and PGE-2 levels (Costa 2012; Harris et al. 2005).

Black et al. demonstrated reduction in the occurrence of actinic keratoses and nonmelanoma skin cancers in patients who followed low fat and isocaloric diet (with greater omega-3 intake) compared with patients who consumed higher percentages of fat, who showed a higher risk of developing squamous cell carcinoma (SCC) (Costa 2012). Another study also linked high levels of arachidonic acid in biological membranes with a higher risk of SCC, in contrast to reduction in the risk associated with high levels of palmitic and palmitoleic acids (Costa 2012; Harris et al. 2005).

Essential FA as Permeation Agents

FA, such as oleic acid and LA, are able to be placed between the hydrophobic tails of the lipid bilayer, disturbing their settings, increasing its fluidity, and decreasing the resistance to permeants, what promotes the absorption and enhances drug and cosmeceutical penetration through the stratum corneum (Costa 2012).

Ingredients of Plant Origin: Plant Extracts, Vegetable Oils, Butters, and Vegetable Waxes

Active ingredients obtained from plants have been very presently valued, which affords botanical-based products to be a conscious and sustainable alternative to cosmetics and cosmeceuticals (Costa 2012; Aburjai and Natsheh 2003; Balandrin et al. 1985). Consumers are more demanding and discerning about the quality of the product consumed, and the concern in using natural products that do not harm nature or

animals contributes to the growth of the wellness industry (Aburjai and Natsheh 2003; Balandrin et al. 1985).

Phytocosmetic is defined as the science of Cosmetology that studies the application of the active ingredients extracted from plant species for the benefit of hygiene, aesthetics, correction, and maintenance of normal, healthy skin (Balandrin et al. 1985). Vegetable ingredients have been included in several preparations with different characteristics and may be classified as astringents, emollients, moisturizers, toners, flushing compounds, tranquilizers, anti-inflammatory, antioxidants, anti-aging, aromatic, dyeing, detergents, antiseptics, antisseborreic, sunscreens, and anti-cellulite (Costa 2012).

In order to make sure about the efficacy and safety of topical use of these ingredients, it is carefully necessary to evaluate the botanical species used, the vegetable ingredient concentration and the finished products, the application area, and the preparation process in which it was submitted (Costa 2012; Balandrin et al. 1985).

Essential Oils

They are highly volatile substances and have great olfactory perception, being found abundantly in plants, mosses, algae, and lichens (Aburjai and Natsheh 2003; Balandrin et al. 1985; Bizzo et al. 2009). They are used mainly as flavors, fragrances, and fragrance fasteners (Bizzo et al. 2009). According to the odoriferous class, the following olfactory notes are recognized: fruity, floral, green, musk, amber, wood, spicy, and marine (Bizzo et al. 2009).

Vegetable Extracts

They are ingredients used in shampoos, soaps, creams, lotions, make-ups, perfumes, and dentifrices and may be employed in the form of purified extracts or crude extracts, as an active isolated source (Aburjai and Natsheh 2003; Balandrin et al. 1985; Freitas 1990). Fruits, blossoms, leaves, roots, seeds, and husks are used in the manufacture of plant extracts with different biological properties (Freitas 1990). Its cosmetic and cosmeceutical properties include: moisturizing, astringent, toning, anti-inflammatory action, antiseptic, vasoprotective and regenerating, improvement of acne and seborrhea, soothing effects, flushing, revitalizing, refreshing, soothing, and decongestant (Freitas 1990).

Oils, Butters, and Vegetable Waxes

Vegetable oils and butters are triglycerides-enriched extracted from vegetables, which are formed mainly of UFA (oils) and SFA (butter) (Costa 2012).

Larger families are considered important sources of oil plants, such as *Asteraceae, Euphorbiaceae, Papaveraceae, Sapindaceae, Simaroubaceae*, and *Leguminosae* (Aburjai and Natsheh 2003; Balandrin et al. 1985). The oil can be produced from the pulp and/or seed, depending on the species, and is composed mostly by LA, linolenic, oleic, palmitic, and palmitoleic (Aburjai and Natsheh 2003; Balandrin et al. 1985). Vegetable oils, in the cosmetics industry, are chemically modified and form the basis of emulsifiers, emollients, thickeners, and filmogenic agents (Costa 2012). Waxes are complex mixtures of lipophilic compounds having average molecular weight, with organic primary barrier function, preventing the evaporation of water contained in the body (Costa 2012; Aburjai and Natsheh 2003). Since they are solid ingredients, as well as flexible at room temperature, they are incorporated into products to increase the rigidity and strength of some products (Costa 2012; Aburjai and Natsheh 2003).

Conclusions

Cosmeceuticals are already considered a reality for the dermatological prescription. As far as cosmeceutical manufacturers have invested too much money and scientific efforts to launch not only more efficient but also safer products in the market, it is time to know that they have obtained acceptance from costumers as well. Those facts are, indeed, the stepping stone to make such class of products stronger and stronger in science and more and more popular among lay people. Undoubtedly, it could make cosmeceuticals no longer to have a specific

regulation in the most important sales market around world.

Take Home Messages

1. Cosmeceuticals represent an expanding class of products; in fact, about 90% of all cosmetics sold in the world are cosmeceuticals.
2. From a dermatological point of view, cosmeceuticals are considered as products containing biologically active substances and ingredients with beneficial effects on the skin, interfering positively on skin physiology.
3. Cosmeceuticals have no therapeutic claims but may have preventive effects beyond beautification.
4. The cosmetic and cosmeceutical formulations are composed of two main parts: the structural portion (vehicle) and functional portion (actives).
5. The efficacy and safety of these products are being increasingly questioned and studied.
6. Cosmeceuticals classes include: antioxidants, hydro acids, retinoids, peptides, miotensors, muscle relaxants, dermal fillers, growth factors, topical enzymes, glycan inhibitors, fatty acids, and ingredients of plant origin.
7. Cosmeceuticals are already considered a reality for the dermatological prescription.

Cross-References

- ▶ Approach in Photodamaged Skin, Melasma, Acne, and Rosacea
- ▶ Chemical and Physical Sunscreens
- ▶ Evaluation and Classification of Aging
- ▶ Oral Photoprotection
- ▶ Photoprotection: Concept, Classification, and Mechanism of Action
- ▶ Skin Anatomy, Histology, and Physiology

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Nutraceuticals in Dermatology

Flávia Alvim Sant'Anna Addor and Flávia Naranjo Ravelli

Abstract

Dietary factors play an essential role in cutaneous homeostasis since they supply the nutrients necessary for good cellular functioning. Any shortage of these elements can lead to dysfunctions of the cutaneous structure, often hard to identify, since the clinical condition is oligosymptomatic. Nutraceuticals are associations of nutrients with benefits and synergistic effects. They act not only in response to any minor shortage of micronutrients but also in phenomena at the cellular level, associated with aging, dermatoses, and the cellular cycle.

Keywords

Nutraceuticals • Antioxidants • Vitamins • Aging • Probiotics

Contents

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Introduction

The cutaneous system consists of a complex that includes the skin and its structures, which has the objective of protecting the individual and allowing his/her interaction with the environment, as well as supporting his/her homeostasis and immune system. As the first barrier to the environment, its defensive and regenerative capacities are extensive. The epidermis and its structures are made up of cells with high mitotic rates, exhibiting high proliferation and physiological differentiation (Kierszenbaum and Tres 2012).

This interaction with the environment demands specific physicochemical and biological defense mechanisms, which based on a continuous interaction with the environment, exhibit a greater or

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lesser need for cellular homeostatic mechanisms, such as antioxidant mechanisms (Guaratini et al. 2007).

Dietary factors play an essential role in this homeostasis since they supply the nutrients necessary for good cellular functioning.

Any shortage of these elements, even if minor, but chronic, can lead to dysfunctions of the cutaneous structure, often hard to identify, since the clinical condition is oligosymptomatic.

In cases of greater environmental stress, however, as seen in photoaging, the role of antioxidant molecules is essential in preventing and repairing photodamage (Sies and Stahl 2004).

On the other hand, some foods, due to their chemical constitution and proportion of nutrients and bioactive molecules, also demonstrate physiological activity in organic tissue, including the skin (Breslow et al. 1995). Lycopene is an example of these foods, combining antioxidant, anti-inflammatory, and DNA-protective properties (Breslow et al. 1995; Offord et al. 2002).

Another research trend in nutrition and skin relates to the association of nutrients with documented benefits, with consequent promoting of effects (synergistic effect) in physiological concentrations. These associations are known as **nutraceuticals**.

Nutraceuticals act not only in response to any minor shortage of micronutrients but also in phenomena at the cellular level, associated with aging, dermatoses, and the cellular cycle (Boelsma et al. 2001).

Basic Concepts

The term nutraceutical, similarly with "cosmeceutical," refers to foods and nutrients that, in addition to their actual nutritional value, promote health and prevent illness: the so-called functional foods, complex molecules (phytoextracts), microorganisms and related substances (probiotics, prebiotics, and symbiotics), as well as vitamins and trace elements (Food Nutrition Board and Institute of Medicine 2000).

Its use in nutritional doses (RDI or recommended daily intake) promotes greater safety of use, preventing risk of toxicity and hypervitaminosis, as well as drug interaction. Table 1 illustrates some of the main nutrients of dermatological interest in DDR, in accordance with RDC ANVISA Resolution 269 - 09/22/2005:

The association of ingredients in the formulation should be developed in a way that allows a synergy of mechanisms and a wider effect. It is known, for example, that the association of doses of vitamins E and C in physiological concentrations, associated with other antioxidants, promotes antioxidant action in photodamage greater than their separate use in high doses (Addor et al. 2013).

Based on in vitro and in vivo studies, possible synergies have been seen between the molecules that promote greater efficacy, while maintaining a greater safety margin; thus, clinical studies are needed to determine the minimum time of use to obtain the clinical effect.

It is important to remember that concomitant use of nutrients orally and topically is not exclusive, but complementary; topical use provides greater support to the target cell, as long as penetration of the skin barrier is ensured. On the other hand, oral use provides a more generalized and long-lasting effect in other adjacent cells and tissues than the topical product (Poljsak et al. 2013).

Background

Historically, certain foods have been used to reduce the risk of illness for thousands of years. Around 2500 years ago, Hippocrates already prescribed this in one of his celebrated phrases when he said: "make food your medicine." However, greater interest in this matter only began at the end of the last century, in the 1990s, when the term "functional food" was adopted. Research intensified and the concept of functional food came to the attention of the

Table 1 Main nutrients of dermatological interest

Nutrient	Recommended daily allowance (RDA)	Effects described
Vitamin A	600 mcg	Antioxidant Regulates keratin synthesis Increases expression of procollagen
Vitamin B1	1.2 mg	Cofactor in various cellular metabolic processes: protein synthesis, use of nutrients: lipids, carbohydrates and proteins
Vitamin B2	1.3 mg	
Niacin	16 mg	
Panthothenic acid	5 mg	
Vitamin B6	1.3 mg	
Vitamin B12	2.4 mcg	
Vitamin C	45 mg	Antioxidant Cofactor in production of collagen
Vitamin E	10 mg	Antioxidant Cellular synthesis and metabolism of keratinocytes Inhibition of cyclooxygenase 2 (COX-2)
Folic acid	240 mcg	Coenzyme in numerous amino acid metabolic reactions and nucleic acid synthesis Skin appendages integrity
Magnesium	260 mcg	Cofactor in protein synthesis
Iron	14 mg	Tissue oxygenation: epidermis renewal and healing
Zinc	7 mg	Antioxidant Anti-inflammatory
Silicon	–	Reduces activity of prolyl hydroxylase: acts in skin repair and synthesis of collagen and elastin Improves skin mechanics properties (firmness and elasticity)
Biotin	30 mcg	Cofactor in metabolism of carbohydrates and lipids in keratinocytes

general public as well as researchers who had not previously been involved in this area of study (Siro et al. 2008).

Japan was the first country in production and commercialization of functional foods, known as Foshu, "Foods for Specified Health Use." The Food and Drug Administration (FDA) in the United States regulates functional foods based on the use intended for the product, in the description provided on labels or in the product ingredients. Based on these criteria, the FDA classified functional foods in five categories: food, food supplement, food for special dietary uses, medicine, or drug food (Noonan and Noonan 2004).

In Brazil, the rules were established in 1999; the industry should obey the legislation of the Ministry of Health and the National Health Surveillance Agency (ANVISA), which establishes standards and procedures for registering functional foods and/or ingredients. To obtain a registration for a food with alleged functional and/or health promoting properties, a quite detailed technical-scientific report must be prepared, demonstrating the benefits and safety of using this food (ANVISA 1999).

Classification

Although there is no formal classification, didactically, the main ingredients used in nutraceuticals of a dermatological interest can be grouped in the following way:

Functional foods/ nutrient molecules	Lycopene, Lutein, Coenzyme Q10 Soybean isoflavones, green tea extract, resveratrol, silymarin, delphinadin
Probiotics	Strains of lactobacillus and bifidobacterium
Trace elements	Zinc, iron, selenium, magnesium, organic silicon
Nutrients themselves:	
Vitamins	Ascorbic acid, tocopherol, complex B vitamins, retinol, carotene
Amino acids	L-arginine
Fatty acids	Omega 3, omega 6, omega 7

The doses and associations may vary considerably, and each association should be clinically proven, since the combinations can increase effects. Trace elements and vitamins are always used at up to 100% of the recommended daily intake (RDI).

Main Dermatological Indications

Aging

The aging process is frequently accompanied by a decline in ingestion and benefit from nutrients, both from the physiological reduction in absorption and metabolization (Grassi et al. 2011), and from capture itself.

Söderström and collaborators (Söderström et al. 2012) evaluated 1770 patients over 65 years of age and found that only 35.5% had adequate nutrition conditions. The main factors listed were long period of nighttime fasting, few meals per day, and difficult access to independent preparation (Söderström et al. 2012).

At the same time, this phase is marked by an increase in oxidative phenomena, due to chronic inflammatory situations, as well as factors such as exposure to solar radiation, alcohol, and tobacco, which demand more from the antioxidant systems that are also in decline (Poljšak and Dahmane 2012).

In addition to the nutrients with antioxidant action themselves, the molecules most used in supporting care in aging, particularly for the skin, are listed below (Table 2):

Atopic Dermatitis

The preventive potential of the atopic condition in pregnant women with atopical antecedents who used probiotics is well documented (Baquerizo Nole et al. 2014; Foolad 2014).

Post-natal use also appears to have positive effects; however, an analysis of the work is compromised, since the species dependent effects, each should have its action mechanism clarified. The association of strains appears to have a synergetic effect (SO et al. 2014).

The use of vitamin D has also been evaluated, demonstrating a reduction of EASI in some studies; however, there is still insufficient data to justify current use (Hata et al. 2014; Bronsnick et al. 2014).

In the same way, some oils rich in omega 3 fatty acids, particularly fish oil, with a possible anti-inflammatory effect that helps restore the epidermal barrier, still do not have a level of evidence sufficient for formal indication. Their use as adjuvants is being studied with promising results (Mohajeri and Newman 2014).

Telogen Effluvium

The correlation between telogen effluvium (TE) and nutritional insufficiency is well known (Rushton 2002; Mulinari-Brenner and Bergfeld 2002; Grover and Khurana 2013).

Alterations in zinc metabolism have a fundamental role in the hair cycle leading to a TE condition and possibly other forms of alopecia (Kil et al. 2013).

Zinc is involved in the synthesis of proteins and nucleic acids and has an important role in several metabolic routs and cellular functions. Specifically in the hair follicle, zinc is a powerful inhibitor of the hair follicle's regression in animal models (Plonka et al. 2005).

Vitamins such as ascorbic acid, folic acid, vitamin E, and biotin also exert direct or indirect roles in the hair cycle for they act on metabolic processes involving protein synthesis or hormone expression or are synergistic with other trace elements, such as zinc and vitamin C (Addor et al. 2014).

Table 2 Main compounds from food in aging

Main molecule/ source	Some of the effects studied	Dose studied	References
Polyphenols			
Epigallocatechin (Green tea)	-Inhibition of erythema and UVB-induced carcinogenesis -Reduction of proinflammatory interleukins	300 – 400 mg of polyphenols, equal to 600 – 800 mg of 50% standard extract	Kim et al. 2013; Chung et al. 2003
Genistein (soybean)	-Inhibits UVA-induced DNA damage -Reduced formation of skin carcinogenesis	8–12 mg/d	Iovine et al. 2014; Afaq and Mukhtar 2006
Resveratrol (grapes)	-Inhibits inflammation and UVB-induced edema	5–30 mg/d	Liu et al. 2015
Carotenoids			
Lycopene (tomato)	-Inhibits oxidation of collagen and expression of metalloproteinase	8–15 mg/d	Costa et al. 2012; Darvin et al. 2008; Addor 2011
Lutein (fruits and vegetables)	-Absorbs photodamage in the visible light range (blue) -Inhibits peroxidation of lipids. -Diminishes inflammation and immunosuppression induced by ultraviolet radiation -Inhibits photocarcinogenesis (at least in one animal species)	6–20 mg/d	Addor 2011; Meinke et al. 2013

Likewise, iron plays a fundamental role in the nutrition of the hair follicle and women with iron deficiency are at risk of hair loss with telogenization (Moeinvaziri et al. 2009).

Biotin supplementation improves the quality of keratin in the hair of animal models, even in the absence of apparent deficiency (Mock 1991).

In diffuse hair loss associated with telogen effluvium, the combination of biotin and zinc was studied with favorable results (Shrivastava 2009).

Psoriasis

Observational studies have shown the safety and efficacy of oral vitamin D supplementation in the treatment of psoriatic lesions and psoriatic arthritis (Fu 2011), although there is not yet a consensus on dosage or time of use.

Other nutrients, such as folic acid and polyunsaturated fatty acids, are being studied (Murzaku et al. 2014).

Other Possible Indications

Healing, Nonmelanoma skin cancer, Melanoma, Acne, Seborrheic dermatitis (Stechmiller 2010; Maier et al. 2013; Katta and DN 2015; Xia et al. 2006; Tong and Young 2014; Burris et al. 2013; Melnik 2012; Brenner and Horwitz 1988; Arslan et al. 2009).

Conclusion

Nutrients are effectively important in the prevention and even control of physiological processes, such as aging and the types of pathologies commented on here.

The use of nutraceuticals for diverse skin conditions has been shown to be a safe and effective option when used as an adjuvant in treatment. The nutrients chosen should have clinical studies of efficacy justifying their use.

Take Home Messages

- The association of nutrients with documented benefits, with consequent promoting of effects (synergistic effect) in physiological concentrations are known as **nutraceuticals**.
- Nutraceuticals act not only in response to any minor shortage of micronutrients, but also in phenomena at the cellular level, associated with aging, dermatoses, and the cellular cycle.
- The use of nutraceuticals in nutritional doses (RDI or recommended daily intake) promotes greater safety of use, preventing risk of toxicity and hypervitaminosis, as well as drug interaction.

Cross-References

- ▶ Approach in Photodamaged Skin, Melasma, Acne, and Rosacea
- ▶ Chemical and Physical Sunscreens
- ▶ Evaluation and Classification of Aging
- ▶ Oral Photoprotection
- ▶ Photoprotection: Concept, Classification, and Mechanism of Action
- ▶ Skin Anatomy, Histology, and Physiology

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Issues Concerning Safety of Topical Cosmetics and Nutraceuticals

Paulo Notaroberto and Bhertha Tamura

Abstract

There are hundreds of cosmetics and orally taken products not included as drugs in the market, even those that promise an additional therapeutic effect as lightening the skin, improving acne, and smoothing rhytides. The list of nutraceuticals is even greater especially when the so-called dietary supplements are included. There are numbers of papers and health alerts referring dangerous substances that are added to these products; some were exclusive from a specific country, but the globalization led to a mixture of all kinds of them being commercialized all around the world. Alerts should be taken seriously and the population should be also notified about this serious matter. We try to discuss about them, and although the list of substances is enormous and some adverse events yet to be described, it could be of interest to alert the patients about their choice. Each country has a list of forbidden formulations and chemicals; some are very rigorous and others still tolerant. We talk in this chapter the majority of them, but some of the regulatory issues are based in Brazilian ANVISA (National Health Department).

Keywords

Nutraceuticals • Cosmetic • Adverse events • Safety • Contact dermatitis

Contents

Introduction

Cosmetics are defined as any product that can be applied on the skin surface, mouth, hair, or nails with the aim of cleaning, coloring, decorating, providing a pleasant smell or giving protection,

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and improving the appearance and attractiveness acting on the skin or its functions without affecting the body itself. We must add the fact that cosmetics should be applied to intact and healthy skin and that they were not supposed to induce skin response or interfere with the skin physiology. These products are always present in daily life and must be safe. The positive impact of these products on the quality of life of modern society is undeniable, so the occurrence of any adverse event is always unwanted and unexpected. Moisturizers, perfumes, lipsticks, all kinds of makeup, shampoos, deodorants, hair dyeing, and others are examples of the list of an everyday personal care.

In the last decades, cosmetics have become an important adjunctive tool in the management of cosmetic conditions such as rejuvenation and clinics, like acne and atopic dermatitis. Even in indications taken as merely aesthetic, modern cosmetics stimulate some kind of response in the human skin, such as stimulating collagen synthesis by fibroblasts in the case of products used for skin aging and tyrosine inhibitors in the case of bleaching creams. The boundary between these kinds of products and a really effective drug is not clear. This class of products is called cosmeceutical or active cosmetic and is known by ordinary people as a "cosmetic of result." Cosmeceuticals need simple clinical trials to demonstrate safety and performance before being launched (Vigan and Castelain 2014; Dureja et al. 2003).

Oral supplements with vitamins and active compounds have been widely studied and marketed in the last years to be added to topical treatments with the purpose of enhancing the results. Those oral products are called nutraceuticals (Krasteva et al. 2010).

It is noticed that cosmetic treatments have become more effective at the expense of products composed of most powerful assets. On the other hand, it is expected that a cosmetic product should have a high safety profile once it can be purchased without a medical advice. Companies that produce or market cosmetics have the responsibility to ensure the safety and quality of the products. Health authorities have a duty of preserving the health of the population and, therefore, are continuously monitoring any deviation of quality in products on the market as well as supervising to ensure compliance with legal requirements of good practice.

Companies that produce or market cosmetics are responsible for collecting and technically analyze any adverse event information of their products and compare to the safety information available on global databases. They should share with the regulatory health authorities all the informations about adverse events of a particular product in order to take the necessary actions to ensure the health of the population.

The set of actions of monitoring, identifying, evaluating, analyzing, classifying, and reporting adverse reactions (or events) related to cosmetic products is called cosmetovigilance.

Cosmetics

There are reports that some substances might be toxic to humans, and the thyroid gland might be affected by phthalates and tricosane, for example. The worst effects occur at adolescents. Cosmetics should not cause allergy, and there are specific pattern tests but not referring to cancer.

The most common long-term undesirable side effect is irritation and or sensitization of the skin, and even worst, the real allergic reaction is caused mostly by the fragrance and or preservatives.

The allergic reaction might evolve with erythema, ardor, irritation of the skin, and itching and results sometimes in blisters and vesicles. The compounds that mostly sensitize the skin are the preservative as methylisothiazolinone, phthalates family (di-n-butyl phthalate, di (2-ethylhexyl phthalate – that can cause cancer), paraben mix, formaldehyde, quaternium 15, chloromethylisothiazolinone/methylisothiazolinone mix, methyldibromoglutaronitrile, diazolidinyl urea, imidazolidinyl urea, DMDM hydantoin, 2-bromo-2-nitropropane-1,3-diol, iodopropynyl butylcarbamate, benzalkonium chloride, sodium metabisulfite, p-phenylenediamine (hair dyes), colophony (main contents of pine resin), and lanolin alcohol (emollients), for example. Some of these substances are forbidden in many countries but are still commercialized and are included in

famous and expensive products in the market. Another substance is benzophenone that can also be detected in urine; there are reports of sperm DNA changes using products with butylparaben, and we recommend a review in the internet database of the Environmental Working Group (skin deep Safe Cosmetics Database) for those that want more details and an up-to-date information.

In Brazil one of the most recent concerns was the use of formaldehyde and its derivative, the methylene glycol that is used for hair care, pretending not to be harmful. But, under heat it changes to the toxic form of formaldehyde used for hair straightening. Besides allergic reaction and skin irritation, in the formaldehyde group, there are derivatives as 3-diol imidazolidinyl urea, DMDM hydantoin, quartenium-15, nitropropane-1, formalin, methanal, methyl aldehyde, methylene oxide, morbicyde acid, and oxymethylene that are carcinogens and can cause headaches, mucosal and eyes irritation, chest and joints pain, depression, tiredness, dizziness, and immunity changes. They can be used as compounds of disinfectants, hair, nail, shower, makeup removers, facial masks, powders, antiperspirants, and other body care products. We cannot forget heavy metals and ammonium included in dyes for hair that can burn the skin and the scalp also leading to hair loss.

Asthma can be unleashed or worsened by salicylic derivatives, and respiratory problems can occur in patients that are sensitive to shower gel (alkyl aryl sulfonate). Some cosmeceuticals might promise to rejuvenate the skin but they might give an initial good looking effect but, as a long-term effect, accelerate the aging by reducing the protective barrier of the skin even facilitating the sensitization of the skin for other products. We do also use a lot of products that in contact with our eyes, in one way or other, can lead to conjunctivitis and irritation of the eyes and nose (fragrancies), stop the growth, or lead to eyelash losses and bacterial contamination and even resulting in blindness.

There are numerous everyday products that we use constantly and papers reporting blood test alterations in cosmetic laboring at cosmetic industries. Others are revealing chance of bacterial colonization of the skin due to contaminated makeups. Makeups can also provoke pore obstruction, discromias, spots, post inflammatory pigmentation, redness, and acne.

An average professionally active lady might be exposed to a range of 175 different substances daily and 20 different beauty products adding 2.5 kilos of chemical substances per year, with an index that can reach 60% of absorption through the body (Lefebvre et al. 2012; Dreno et al. 2014; Krecisz et al. 2015; Pauwels and Rogiers 2010; Moretti and Velo 2008; Sautebin 2007; Di Giovanni et al. 2006; International Agency for Research Organization. IARC Monographs Carcinogenic Risks to Humans 2006; Instituto Nacional do Câncer 2006; U.S. Department of Labor. Occupational Safety and Health Administration 2011; National Toxicology Program, Department of Health and Human Services. Services Report on Carcinogens, Twelfth Edition 2011; Agencia Nacional de Vigilância Sanitária 1999; International Programme on Chemical Safety (IPS): Chemical Safety Information from Intergovernmental Organizations (INCHEM) 1993; Bons et al. 2010; Nohynek et al. 2010).

There is not a global regulation to control and test the cosmetics; we suggest the following sites for doubts: www.fda.gov, www.fda.gov/cosmetics/defaut.htm/, www.cosmeticsinfo.org, www.cosmeticdatabase.com and www.livestrong.com/article/160667/-what-are-the-effects-of-makeup-on-the-skin/#ixzz2o3lfelfn.

Nutraceuticals

Nutraceuticals are treated differently in different jurisdictions, and the term is a combination of the words “nutrition” and “pharmaceutical,” which was coined in 1989 by Stephen L. DeFelice, and the term is applied to products that range from isolated nutrients (like vitamins and minerals), dietary supplements and herbal products, specific diets, and processed foods such as cereals, soups, and beverages. In some countries it is marketed as a food (functional food) or a drug, is generally sold in medicinal forms not usually associated with food, and is demonstrated to have a

physiological benefit or provide protection against chronic disease; in other countries, the term depends upon the ingredients while in others as organic or exotic ingredients, but in summary the worldwide market moves billions of dollar and is defined as dietary supplements and functional foods and beverages.

Nutraceuticals (phytochemicals or functional foods) are natural bioactive, chemical compounds including vitamins, herbs, minerals and other botanical, amino acids, and any dietary substance, enzymes, organ tissue, glands, and metabolites for use by humans to supplement the diet and that may claim to prevent chronic diseases, improve health, delay the aging process, increase life expectancy, or support the structure or function of the body. They are found in various products emerging from the food industry, herbal and dietary supplement market, pharmaceutical industry, and pharmaceutical/agribusiness/nutrition conglomerates and are taken by mouth as tablets, capsules, softgels, gelcaps, liquids or powders, and tinctures and do not need the US FDA approval.

Functional food concept is actually different from nutraceuticals. The first are food products to be taken as part of the usual diet in order to have beneficial effects that go beyond what are now known as traditional nutritional effects.

Nutraceuticals products are claimed to reduce the risk of cancer, arthritis, osteoporosis, hypertension, high cholesterol, excessive weight, diabetes, digestive upsets, constipation, headaches, macular degeneration, and cataracts and diminish memory and concentration, insomnia, menopausal symptoms, and others.

Nutraceuticals can also be divided into nutrients, herbals, and dietary supplements. Nutrients are substances with nutritional functions as vitamins, minerals, amino acids, and fatty acids. Herbals are concentrates and extracts of herbs or botanical products, and dietary supplements are derived from other products as pyruvate, chondroitin sulfate, and steroid hormone precursors. Dureja et al. 2003 has published an educational forum about developments in nutraceuticals with almost all indications, classifications, and products used at that time, and it is really an interesting report. Although indications are countless, dermatology is a specialty that has an intimate relationship with all other areas, and they conjoint with a lot of diseases and cannot be separated. Any product that is mostly related to rejuvenation, skin, nails, hair, hydration, and even dermatosis might be of interest. Among them, we can list substances that act against cancer (phytosterols, phenolic compounds), with anti-inflammatory effects (garlic, ginseng, lycopene), protein metabolism (sucrose, glucosamine sulfate and chondroitin sulfate), antimicrobial activity (honey, green tea, soybean, probiotics), rejuvenation influence (natural antioxidants), and hormone-like behavior (soy flour, mushrooms) (Krasteva et al. 2010; Berne et al. 2008).

Notifications of Adverse Events

In Brazil, the regulatory health authority is called ANVISA (*Agência Nacional de Vigilância Sanitária* – National Health Surveillance Agency) (Berne et al. 2008) and defined adverse event as any undesired effect in humans due to the use of products under sanitary surveillance. Adverse reactions can range from a mild symptom causing discomfort, like an itch or stinging up, to cases of severe allergic reactions such as contact urticaria and angioedema which may require hospitalization and are life-threatening. The intensity is not only related to symptoms or signs. It is also based on the extension of the skin lesions and the degree of impairment of daily activities. Most of the adverse reactions are mild, self-limited, and totally regressing without leading to any kind of sequel.

The time of use and the onset of adverse reactions can vary widely. The reaction may appear in the first application, progressively, or after long-term use (days, months, or years). Most of the early reactions are related to a direct effect of the product on the skin and are called irritative contact dermatitis or contact dermatitis by primary irritant. Allergic contact dermatitis, contact urticaria, and angioedema are reactions that require prior sensitization and therefore take place after a longer use of the product. Adverse reactions may appear even with the correct use of the product (as required by

the manufacturer) or may occur in inappropriate situations and not recommended for use.

The use of cosmetics by the general population is a habit, and also due to more active and complex formulas, adverse reactions to cosmetic products have become more frequent. Even so, adverse reactions resulting from the use of cosmetics are not frequent reactions and the incidence is low. One must always remember that cosmetics are products developed and tested to have a high safety profile.

Causality Assessment

Many times, the reactions reported by a consumer as being associated with the use of one product might have another cause. Skin diseases can simulate reactions to cosmetics and allergic reactions to other products and can also be confused with cosmetic reactions (e.g., drug reactions or food allergies). The improper use as though as the application of a large amount of a product can lead to an adverse reaction such as irritation; the use on a frequency greater than the daily recommended, using in inappropriate situations (e.g., photoexposure while using a photosensitizing product), and the use without a proper indication (e.g., using anti-acne soap in a dry and sensitive skin) can cause irritant reactions. Many consumers use a thin layer of sunscreen and undergo intense solar exposure. The sunburn resulted from this misuse is often confused with an adverse event to the sunscreen.

In a company that markets cosmetics, the consumer service center (call center) is the main channel of communication with the consumer and is where most reports of adverse reactions income. Companies should also monitor the media and actively contact consumers who report adverse reactions in digital media. The call center should be trained to be able to capture the necessary information for accurate identification of the suspected product and identify the chronology of using and of the appearance of the adverse reaction as well as the description of the signs and symptoms. The call center must also make regular contacts with the consumer for monitoring the follow-up. One can notice that the call center plays a very important role on the cosmetovigilance procedure.

The causality assessment is strictly aimed at analyzing individual cases. All the information collected by the call center relevant to each case are analyzed by a doctor, and the case is classified according to the causality as "very likely," "likely," "questionable," "unlikely," and "excluded". The causality refers to the degree of probability that the product is responsible for the adverse reaction.

The data collected in the cosmetovigilance process by the company provide detecting problems in formulation, manufacturing, or communication with the consumer and improve future launchings by developing more effective and safe products.

Cosmetovigilance in the Mercosul

From December 31, 2005, the implementation of a cosmetovigilance system by manufacturers or importers of cosmetic products became legally binding. The importance of the implementation of cosmetovigilance is justified by the free access to cosmetic products by the consumers, using in early ages, and the use for long periods and with multiple products simultaneously, in compliance with the responsibility of the Health Regulatory Agencies to protect the health of the population.

The cosmetovigilance program in companies assesses the probability of the reported adverse reaction to be related or not to the use of a suspected product and to assist the consumer when the causality is proven. The cosmetovigilance system ANVISA documents, investigates, and analyzes the adverse event reports. This investigation is under confidentiality of the data of the parties involved, and the data become part of a database relating to cosmetic products, their raw materials, frequency of adverse events, and the safety. The data obtained allows taking regulatory actions, such as the labeling information modification, publishing alerts and guidelines for rational use, and reviewing the raw material concentration and indications of use in cosmetics. Batch recalls, product suspension, and even the cancelation of

registration can be performed when severely and frequently adverse reactions occur.

Nutraceuticals Areas of Concern

The lack of scientific evidence and a standardization of the proper quantification, duration, evidence of results, and a clear protocol to classify, select, measure, origin, the way the raw material was produced, how it was industrialized, levels of contamination (bacteria, fungus, pesticides), and, as a summary, absence of quality control leads to a discredit and a lot of questions and doubts about the true importance of these products.

As soon as some kind of regulatory control can be established, we just do not know how to indicate and how to prescribe and believe they can be efficacious or not and if they can help, interact, or interfere with the routine medical prescription for all different diseases. Although promising, it is only beginning to be taken seriously and might play an important rule for the future as prevention and treatment, and it tends to emerge and be taken seriously in the future.

Conclusion

The market for cosmetic products and nutraceuticals has undergone significant growth in recent decades. The manufacturing companies began to use more effective raw materials in order to obtain better clinical results. The massive use of them associated with the potentially stronger products has caused an increase in the incidence of adverse events related to the use of cosmetics as though as nutraceuticals. Companies that are responsible for the products that they sell and health authorities are responsible for monitoring and ensuring the health of the population. Thus, the cosmetovigilance as though as the population health administration of each country might control at least every adverse event through post-marketing surveillance activities detecting any problems related to these products helping the companies and the government to take the necessary actions in each case. The information collected through the cosmetovigilance and food administration system also allows companies to develop more effective and safer products (U.S. Department of Labor. Occupational Safety and Health Administration 2011; National Toxicology Program, Department of Health and Human Services. Services Report on Carcinogens, Twelfth Edition 2011; Agencia Nacional de Vigilância Sanitária 1999; International Programme on Chemical Safety (IPS): Chemical Safety Information from Intergovernmental Organizations (INCHEM) 1993; Bons et al. 2010; Nohynek et al. 2010; Berne et al. 2008; Salverda et al. 2013).

Take-Home Messages

- Cosmetics are defined as any product that can be applied on the skin surface, mouth, hair, or nails with the aim of cleaning, coloring, decorating, providing a pleasant smell or giving protection, and improving the appearance and attractiveness acting on the skin or its functions without affecting the body itself.
- The worst effects occur at adolescents. Cosmetics should not cause allergy, and there are specific pattern tests but not referring to cancer.
- The most common long-term undesirable side effect is irritation and or sensitization of the skin, and even worst, the real allergic reaction is caused mostly by the fragrance and or preservatives.
- Nutraceuticals are treated differently in different jurisdictions, and the term is a combination of the words “nutrition” and “pharmaceutical,” which was coined in 1989 by Stephen L. DeFelice. The term is applied to products that range from isolated nutrients (like vitamins and minerals), dietary supplements and herbal products, specific diets, and processed foods such as cereals, soups, and beverages.
- The cosmetovigilance as though as the population health administration of each country might control at least every adverse event through post-marketing surveillance activities detecting any problems related to these products helping the companies and the government to take the necessary actions in each case.

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Part V

Procedures in Cosmetic Dermatology

Chemical Peelings: Face

Maria Paulina Villarejo Kede and Luiza Soares Guedes

Abstract

Chemical peel, which is also known as chemical exfoliation, consists on the application of one or more exfoliating skin agents, leading to the destruction of some layers of the epidermis or dermis, followed by the regeneration of the skin. Different substances are used to promote chemical exfoliation, and they should be chosen according to the skin phototypes, to the area, and to the dermatoses to be treated. Usually chemical peels promote skin rejuvenation through the improvement of the skin texture, fine lines, and pigmentation. It can also reduce actinic keratosis and some superficial scars. In this chapter, we are going to discuss different types of peels, mechanism of action, steps of the procedures, indications and contraindication, side effects, and its management.

Keywords

Chemical peel • Exfoliation • Acne • Melasma • Photoaging

Contents

Introduction

Chemical peel, which is also known as chemical exfoliation, consists on the application of one or more exfoliating skin agents, leading to the

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destruction of some layers of the epidermis or dermis, followed by the regeneration of the skin (Fischer et al. 2010).

The appropriate application technique causes a programmed and controlled damage, with immediate vascular coagulation, resulting in the skin rejuvenation through the reduction of actinic keratosis, pigmentation, wrinkles, and some superficial scars (Baker and Gordon 1961; Butler et al. 2001).

The first report on the use of the chemical peels was in 1941, when Eller and Wolf used the technique for the treatment of acne scars. Mackee and Kerp used a similar treatment in 1903. The American interest in this particular field increased with the first reports from the European in 1930 and 1940 (Ayres 1960).

Ayres (1960) and Baker and Gordon (1961) introduced what is known as the "modern age of the chemical peels." Brody and Hailey in 1986 used the combination of two superficial chemical peel agents to perform a medium-depth peel. Mohneit reported in 1989 another technique for the combination of different chemical peels (Brody 2000).

Chemical Peels

The choice of one substance or specific technique depends on lesion depth and dermatologist expertise to avoid excessive exfoliation, deeper than the lesion (Bagatin et al. 2009). When treating minor signs of skin photodamaged or freckles (epidermal lesions), deep exfoliating agent, such as the Baker phenol, causes excessive damage as it reaches the reticular dermis, with high risk of complications. In these cases, superficial or medium-depth agents are able to bring benefits without complications (Stegman and Tromovitch 1984).

Mechanisms of Action

The alterations produced by the chemical peels occur through three different mechanisms (Brody 2000; Albergel et al. 1985):

1. The removal of the stratum corneum, promoting epidermal growth. Even very light desquamation that does not produce epidermal necrosis may cause the epidermal thickening.
2. Destruction of specific damaged skin layers, which causes the replacement for a "better skin," with greater aesthetic characteristics. This mechanism is very important when we want to treat pigment disorders and actinic keratosis.
3. Induction of an important inflammatory reaction associated with necrosis caused by the exfoliating agent. The activation of inflammatory mediators (poorly understood mechanism) leads to new collagen production and dermal remodeling.

Classification

The chemical peels are classified into four groups, according to tissue necrosis depth caused by the exfoliating agent (Brody and Hailey 1986).

Peel Levels (Kede and Sabatovich 2015)

1. Very superficial (exfoliation): Those peels cause skin thinning. Remove stratum corneum and do not cause any damage below the stratum granulosum.
2. Superficial (epidermal): Those peels produce a full- or partial-thickness epidermal necrosis, anywhere in between the stratum granulosum and the basal cell layer.
3. Medium (papillary dermis): Those peels produce epidermal necrosis and partial- or full-thickness papillary dermal necrosis.
4. Deep (reticular dermis): Those peel produce necrosis from the epidermis until the initial layer of the reticular dermis.

This classification helps with the choice of the chemical agent according to the depth of the lesion that we want to treat. Nevertheless, that classification is not definitive, and we must have in mind that each chemical agent may change its mechanism of action depending on several factors (Brody 1989a, b).

Factors that May Affect Peel Depth

The factors that might affect the depth of a chemical peel are (Clark and Scerri 2008):

1. The exfoliating agent characteristics (Kede and Sabatovich 2015):
   - Solution type
   - Concentration
   - Number of layers applied
   - Application technique (swab, brush, gauze)
   - Time before neutralization
   - Frequency between treatments sessions
   - Agent manufacturing
2. The epidermal integrity:
   - How did you clean the skin before the procedure?
   - How did you prepare the skin weeks before the peeling?
3. Skin thickness:
   - Skin type – thin or thick, normal, dry or oily
   - Peel area – face or non-facial areas
4. Agent occlusion:
   - Type of occlusion tape
   - Peel area
   - Occlusion duration

Peel Level and Factors that May Affect Peel Depth

The peel depth cannot be defined only by the peel agent, since many other factors (described above) may interfere with the penetration level.

For example, the use of a 25% trichloroacetic acid (TCA) with a swab on the face of a man, with a thick and oily skin, which was not prepared weeks before the procedure, will lead to a superficial epidermal desquamation. On the other hand, if we scrub a gauze with 25% trichloroacetic acid several times on the face of a woman with a thin skin, who had used retinoic acid daily for several weeks before the peeling, the desquamation is going to be deeper and stronger, resulting in a medium-depth peel (Monheit 1989; Nelson et al. 1995).

After the initial epidermal necrosis produced by the application of the chemical agent, one important factor about the chemical damage is the initial migration of the normal keratinocytes from the edges of the injured skin and from the adnexal epithelium reminiscent at the injury basis. After the beginning of the migration, the cellular proliferation at the wound edges increases, in order to produce more cells to the healing process the lesion (Nelson et al. 1995; Clark 1985; Krawczyk 1971).

The facial skin is different from other body areas because of the increased number of pilosebaceous units at each cosmetic unit, leading to a faster epithelization. The nose and the forehead have more sebaceous glands than the cheeks or the temporal area. And that is the reason why the facial healing process always starts from the central facial area to the peripheral area (Collins 1987; Mailbach and Rovee 1972).

The eyelid skin has a dermo-epidermal junction almost linear with a thinner dermis and a delicate network of extracellular matrix. There is only a thin layer of fat tissue closer to the surface, such as the muscle underneath.

On the extensor area of the limbs, the dermis is thicker than on the flexor area.

The deeper is the peel, the higher is the risk of complications and the longer is the recovering period. Actually, the goal is to produce the minimum area of necrosis and at the maximum new tissue stimulation, at the same time. That is the idea behind the protocols of repeated superficial and medium-depth peelings. They have a low risk of complications and lead to progressive benefits that are much more interesting than the one-time superficial desquamation (Collins 1987).

Patient's Selection

We should evaluate each patient, to decide which exfoliating agent will produce the best outcome with the least morbidity, according the indication of the chemical peeling, the patient's lifestyle, the depth of the lesions to be treated, and the skin type.

The main questions to be asked before doing a peeling are summarized in Table 1.

The Fitzpatricks classification (Table 2) allows an evaluation of the pigmentation pattern in

Table 1 Items to be considered during the evaluation of a patient before a chemical peeling

Fitzpatricks skin type
Level of actinic damage and skin aging
Level of sun exposure
Use of cosmetics
Sebaceous gland density – use of oral isotretinoin or exposure to radiation
Previous aesthetic surgery
Smoking
General physical and mental health status
Use of medications
Pregnancy
Herpes simplex
History of hypertrophic scars
Realistic expectations

Table 2 Fitzpatricks skin type

Skin type	Color	Reaction to sun exposure
I	White, very fair	Always burns, never tans
II	White, fair	Usually burns, tans with difficulty
III	Medium	Sometimes burns, usually tans
IV	Olive	Rarely burns, always tans
V	Brown	Never burns, always tans
VI	Black	Never burns, always tans

response to the ultraviolet light and might give information about the ethnic origin.

That information is very useful to predict which patients will have a good result with the peeling and which have a higher risk of pigmentation disorders after the procedure (Garg et al. 2009; Leyden et al. 2011).

All the peelings can be used for the Fitzpatricks skin types I to III. Nevertheless, for patients with skin type I with intense sun damage and neck poikiloderma, we must be careful with the delimitation area between the treated and nontreated skin after peeling, since the treated skin will appear very white compared to the damaged area (Glogau 1994).

The skin types IV to VI represent a higher risk of developing pigmentation disorders.

In some countries, the Fitzpatrick classifications should be used with caution because of the racial mixture.

Actinic Damage and Photoaging Level

If we examine the V-neck area (always exposed to the sun) with the breast skin (sun protected), we can easily observe the cumulative ultraviolet damage, known as dermatoheliosis.

The evaluation of the photodamage status is very important to help choosing the most appropriate exfoliating agent and to plan the number of treatment sessions.

There are two classifications used to evaluate the photoaging (Tables 3 and 4).

In order to plan a better peeling and predict the results, several methods have been described to evaluate the degree of wrinkles. The Fitzpatrick classification is very useful; however, it does not distinguish the static wrinkles from the dynamic ones. When we inform the patient about the expected results, those characteristics should not be forgotten.

About the patient lifestyle, we must advise that the sun exposure should be avoided during the present and also for the future, to keep the benefits achieved with the peeling. Sunscreens must always be used for outdoors activities.

The peeling will not penetrate evenly if the skin is too oily, with or without acne scars. It is necessary to clean the skin in order to remove the excessive oil production, to have a better result (Collins 1987).

We should ask the patient about the present or past use of oral isotretinoin, because it is associated with a higher risk of scars after peeling, since systemic retinoid will increase collagen synthesis and reduce the collagenase production. The result of the inhibition of the collagen degradation could be an excessive accumulation of this protein and the formation of hypertrophic scars. Therefore, after the oral isotretinoin treatment, we should wait at least 6 months to do the medium and deep peels.

The irradiation of the skin causes atrophy of the pilosebaceous units, which delays the epithelization process. In this situation, we should prefer the superficial peels.

Table 3 Glogau classification of skin aging

Group	Classification	Typical age	Description	Skin characteristics
I	Mild	28–35	No wrinkles	Early photoaging; mild pigment changes; no keratosis; minimal wrinkles; minimal or no makeup
II	Moderate	35–50	Wrinkles in motion	Early to moderate photo aging; early brown spots visible; keratosis palpable but not visible; parallel smile lines begins to appear; wears some foundation
III	Advanced	50–65	Wrinkles at rest	Advanced photoaging; obvious discoloration; visible capillaries; visible keratosis; wears heavier foundation
IV	Severe	60 and up	Only wrinkles	Severe photoaging; yellow/gray skin color; prior skin malignancies; wrinkles throughout – no normal skin, cannot wear makeup because it cracks and cakes; severe acne scar

Table 4 Fitzpatrick wrinkle assessment scale

Class	Wrinkle	Score	Degree of elastosis
I	Fine wrinkles	1–3	Mild (fine textural changes with subtly accentuated skin lines)
II	Fine to moderate-depth wrinkles; moderate number of lines	4–6	Moderate (distinct papular elastosis [individual papules with yellow translucency under direct lighting] and dyschromia)
III	Fine to deep wrinkles; numerous lines with or without redundant skin folds	7–9	Severe (multipapular and confluent elastosis [thickened yellow and pallid] approaching or consistent with cutis rhomboidalis)

When the patient was submitted to a rhytidectomy, eyebrow lifting, or blepharoplasty, we recommend a period of 4–12 weeks after surgery to do a facial peeling. To avoid scarring complications such as the ectropion, eclabium, and hypertrophic scar formation, the peeling should only be done after the complete surgery wound healing.

If the patient has smoking habits, we have to tell him the wrinkles around the mouth might reappear a few months after the peeling, unless he stops smoking. Besides, the cigarette smoke will produce free radicals that damage the small blood vessels and produce degradation of the skin collagen and elastin.

There are only a few definitive contraindications to all the types of chemical peels. Superficial exfoliation is usually well tolerated in every skin types (Cuce et al. 2001).

It is also important to investigate if the patient is using any oral medication. For example, the use of hormonal replacement therapy for menopause or oral birth control pills might cause a sensibilization to ultraviolet radiation and produce post-inflammatory hyperpigmentation. The use of nonsteroidal anti-inflammatory drugs or oral anticoagulants does not affect the procedure (even for deep peels), because the peel causes immediate coagulation.

Although some peels might be used, as adjuvant therapies for acne and rosacea, the exfoliation over acne inflammatory lesions will produce a deeper desquamation in that area (Cuce et al. 2001).

Patients under physical and mental stress, who scratch the skin very often, carry a higher risk of producing a damage to the desquamating skin and severe complications.

The pregnancy is not an absolute contraindication; nevertheless, there are not enough clinical studies with the use of the chemical agents during this phase of life, and for this reason, chemical peels should not be used.

If the patient has a clinical history of chronic herpes simplex, an antiviral-specific drug

(acyclovir, valacyclovir, famciclovir) should be used as prophylaxis, during the medium and deep peels. The first dose should be given in the same day the peel will be done, and the whole treatment can last from 5 to 7 days.

The risk of developing scars after a deep peel is higher compared to a medium depth peel, in patients who have a personal history of hypertrophic scars or keloids. A test in a small facial area could be done, but the response might not be the same as in the whole face.

A complete physical and history evaluation of the patient ensures a good doctor-patient relationship and gives real expectations that will help after the procedure.

Before Procedure

High-definition digital pictures are useful for any aesthetic procedure, at least in three positions: front, right, and left profiles. Very frequently patients forget how they looked before the procedure and point some preexisting "defect" as a new one. In this case, the picture took before helps to show the patient that the "defect" was already there.

It is necessary to fill a complete questionnaire with patient personal information, use of topical or systemic medications, previous diseases, history of herpes simplex, allergies, face and neck surgeries, face lesions (cuts, insect bites, acne), and the previous skin treatment.

It is also important to give the patient information and instructions about the type of peel that will be done, so they understand the procedure and clarify any doubts or concerns.

We must excise or shave every keratotic and vegetating lesion, before the peel.

One month before the peel, the patient should start a rejuvenation treatment, with topical agents like retinoic acid, glycolic acid, bleaching agents, topical vitamin C, 5-fluorouracil, and sunscreens (Darlenski et al. 2010).

The stratum corneum will become thinner with the use of the retinoic acid, causing a deeper and uniform penetration of the exfoliating agent, with a faster epithelization.

The alpha hydroxyacids (AHAs) have a different mechanism of action but will produce a similar effect at the stratum corneum, and therefore the AHAs have a synergistic action with the retinoic acid.

The use of sunscreens and bleaching agents will lower the risk of hyperpigmentation.

There are medications that might affect the epithelization process. Zinc, for example, stimulates directly the epithelization. The systemic retinoids increase the collagen synthesis and inhibit the collagenase activity, which increase the risk of hypertrophic scars. Steroids do inhibit the inflammation, which has a major role at the healing process. Estrogens and oral birth control pills increase the risk of post-inflammatory hyperpigmentation (Kede and Sabatovich 2015).

The pre-peel clinical protocol should comprise the following items:

- Before pictures (front, right, and left side) – high quality and standardized
- Checklist with all the topics that should be reviewed during the procedure
- Informed consent form
- Printed instructions to follow after the peel

Theoretically, any patient that will be submitted to a procedure with a potential risk of complication should sign an informed consent form.

One of the most important things to do before the chemical peel is to prepare the skin for 2 or 3 weeks. The goals are:

- To reduce the healing time, because the epithelization process will be faster and this reduces the risk of infection and early desquamation of the skin
- To produce a more uniform penetration of the chemical agent, because the amount of dead cells is diminished and the stratum corneum is thinner
- To show the patient the need of keeping a routine of skin care and test for any kind of allergy to the agents used
- To reduce the risks of post-inflammatory hyperpigmentation with the use of bleaching treatments before the procedure

Before using the chemical peel agent, ask the patient the following questions:

- Did you have any facial hair removal recently?
- Were you submitted to a face or neck surgery recently?
- Were you under treatment with oral isotretinoin in the last 2 months?
- Have you been using the rejuvenation protocol prescribed?

If it is a medium-depth or deep peel and the patient has a history of herpes simplex, we should start prophylactic medication in the day before the peel or in the same day.

Every patient that is submitted to any kind of peel must be very focused about avoiding sun exposure and changing his life routine.

Anesthesia

For superficial and medium peels, there is no need of anesthesia. The pain or the burning sensation during a chemical peel lasts for only a short period, is not constant, and increases as a heat shock. It is important to alert the patient about the discomfort feeling during the peel, but we should also say that is going to be only for a short period of time.

Some doctors will use oral painkillers or sedative drugs for medium-depth peels. The whole procedure might be faster, but risk of systemic reactions and the costs are higher.

The use of topical anesthesia could increase the TCA penetration because it causes vasoconstriction, which decreases the water content at the interstitium and increases the acid concentration.

Procedure

1. List of materials needed to realize the peels (Kede and Sabatovich 2015):
   - Glass recipient to put the peel agent
   - Chemical agent with label and expiration date
   - Neutralizing solution
   - Non-sterile gloves
   - Gauze and cotton
   - Cotton swab, brush, spatula
   - Water
   - Skin cleaning solution
   - Oil removal solution (alcohol and acetone)
   - Small ventilator or fan
   - Digital camera
   - After-peel creams (calming masks, steroid lotions)
2. Precautions during the procedure (Kede and Sabatovich 2015):
   - Always check the label of the acid. The accidental use of an acid with a higher concentration would cause serious reactions.
   - In order to avoid contact of the acid with the eyes or the face, do not open the recipient or prepare the applicator above the patient's face.
   - Keep the headrest raised at 45°.
   - To wash the eyes in case of an accident, we need a bottle of water or saline.
   - Pay close attention to the tearing. If one teardrop runs to the neck area, it could cause desquamation or dilute the acid in this area, leading to a more superficial peel.
   - Check carefully the manufacturer and the quality of the acids, and be sure they have the concentration and pH that you need.

Post-procedure

Healing Process

The wound healing is defined as the interaction of a series of complex events that lead to the recovery of the surface, the reorganization, and the recovery of the elastic resistance of the damaged skin.

The healing steps after the chemical peel are very similar to a conventional surgery:

- Coagulation and inflammation
- Epithelialization
- Formation of the granulation tissue
- Angiogenesis
- Collagen remodeling

The treatment to be prescribed after the peel should be personalized by each doctor. Some doctors prefer to keep the skin dry during the whole healing process, while others will keep the skin humid to increase the water concentration at the wound, to increase the migration speed of the epithelial cell.

The scientific reports are polemic, and we should be aware to the risk of a contact dermatitis if we use too many substances in the same formula.

There are several healing agents that can be used after a peel, although the healing time would be the same: *Aloe vera*; vitamins A, D, and E; vegetal oil; silicon; allantoin; silver sulfadiazine, and Vaseline.

Whatever it is the product that you choose, it has to be something that creates a good environment for the healing process. Keeping the skin moist during the healing phase will avoid the fissures, which could appear with the desquamation, irritation, itching or infection.

The authors usually prefer to keep the skin moist and to use a basic emollient agent, like Vaseline.

Localized Peel

We call a localized peel when it is performed in one single aesthetic unity.

For the superficial and medium-depth peels, the differences in texture and pigmentation in the surrounding areas are minimal. For the deep peels, when we treat only one aesthetic unity, there is a surrounding untreated area with great texture and pigmentation differences.

Nevertheless, for patients with a high level of dermato-heliosis, even with a superficial or medium-depth peel, there will be an area of visible untreated skin. Some techniques will help to avoid this result:

- To apply the peel a little further away of the treated skin using a solution with lower concentration
- To apply a bleaching agent in the whole area
- To apply a weaker peel in the whole area around to avoid areas or lines of demarcation
- To treat the limits of the scalp

Non-facial Body Peel

When we do consider treating non-facial areas, we should keep in mind that those areas have a worst healing process, compared to the facial skin (see chapter "▶ Chemical Peelings: Body").

The epithelialization process that occurs after a peel begins at the surrounding health skin and from the pilosebaceous units, with the proliferation of epithelial cells and lateral migration, until they cover the whole area treated with a new epidermis.

Studies have shown that there are 30 times more pilosebaceous units at the face, compared to the neck and chest area, and 40 times more than the arms and the hand dorsum. For this reason, in those areas with a smaller number of pilosebaceous units, the epithelialization is much slower and longer and might have a higher risk for hypertrophic scars.

Therefore, it is wise to:

- Avoid dermal peels in those areas.
- Consider that most of the non-facial peels are used to treat thin wrinkles and brown spots. Thus, it is better to do repeated superficial peels that will lead to deposition of new collagen at the dermis and improve superficial wrinkles, without the use of the deep peels.
- Consider the extension of those areas and the potential toxicity that the chemical agents could cause.

Peel Frequency

There are recommendations about the frequency that a peel should be repeated according to the depth of the treatment, since the superficial and medium-depth peel are usually applied several times in the same patient to obtain a better final result.

We know that the result depends on the depth of the peel and the epithelialization process. The risk of complications is higher if we do a new peel before the skin is fully recovered.

The interval between the sessions varies according to the depth of the previous peel:

- Very superficial peels (stratum corneum): once a week
- Superficial peels (epidermal): can be repeated every 2–6 weeks, depending on the intensity of the epidermal necrosis
- Medium-depth peels (papillary dermis): can be repeated every 3–6 months

We should never repeat a peel with the same agent or another, if the patient presents any sensibility or persistent erythema, caused by the previous peel.

Results According to the Indications

Results of the superficial chemical peels (what should we expect):

Excelent

- Freckles
- Superficial melasma
- Epidermal pigmentation

Variable

- Solar lentigos
- Deep melasma or post-inflammatory pigmentations

Poor

- Seborrheic keratosis
- Junctional nevi
- Dermal melasma

Results of the medium depth chemical peels (what should we expect):

Excelent

- Freckles, solar lentigo
- Superficial melasma
- Epidermal post-inflammatory pigmentation

Poor

- Nevi
- Exophytic seborrheic keratosis

Complications and Its Management

The risk of complications will increase as the depth of the peel increases too. For the superficial peels, usually complications are those of pigmentation, while for the medium and deep peels, scars could happen and also systemic reactions (depending on the agent).

Pigmentation complications:

- Hypopigmentation
- Hyperpigmentation
- Line of demarcation
- Darkening of a nevi
- Erythema
- Persistent flushing
- Bruises

The premature desquamation of the skin might have complications, with any peel. The necrotic skin layer produced by the exfoliating solution works as a protective dressing, allowing the underneath tissue to heal perfectly. The intentional or accidental early removal of this layer exposes an immature and fragile skin and increases the risk of infections, persistent erythema, post-inflammatory hyperpigmentation, and fibrosis.

The post-inflammatory hyperpigmentation happens when an inflammatory skin response leads to a following pigmentation. It is usually associated with patients of darker skin phototype and with the sun exposure after peel. Nevertheless, less frequently it can occur in patients with fair skin and without sun exposure.

The treatment of the hyperpigmentation might be only with sunscreens, since it should disappear with time, or we can use bleaching agents. The pigmentation can arise right after the peel (after 4 or 5 days) or latter (2 months after the peel).

Every exfoliating agent will produce a clarifying of the skin, since melanin is scattered at the

epidermis and with the desquamation some cells will be eliminated and also some melanin. Nevertheless, as the desquamation level becomes deeper, the degree of depigmentation increases because of the destruction of melanocytes, which could cause an irreversible hypopigmentation.

Some degree of erythema is common with every peel. Although some patients might present some bright red areas right after the peel, they should become pinkish 1 or 2 weeks after the peel. If the erythema persists beyond 3 weeks, we should be aware about the risk of an inappropriate healing process. The treatment should begin immediately with high-potency topical steroids, occlusive steroids, or silicone tapes, to prevent the areas of becoming fibrotic, with hypertrophic scars.

Bruises might occur at the infraorbital area in some patients who presented a strong edema after the peel.

After-peel complications:

- Scars: keloids, hypertrophic scar, atrophic scar, necrosis
- Ectropion, eclabium
- Bacterial infection: *Staphylococcus*, *Streptococcus*, *Pseudomonas*, and toxic shock syndrome
- Viral infection: herpes simplex, warts
- Fungal infection: *Candida albicans*

Fortunately the infections associated with the peels are rare, but the risk increases with the depth of the peel. This is because the deeper desquamations will form more crusts, which are more susceptible to bacterial colonization, compared to the peel without the crust.

Since infections might lead to fibrosis, any infection must be treated promptly.

It seems that the infection causes a deeper lesion than the exfoliating agent, in a way that it is necessary to treat with wide spectrum oral and topic antibiotics. It might be necessary to use wet gauzes embedded with trichloroacetic acid 0.25 or 0.5% and mechanical removal of the crusts by a doctor, in cases with thick crusts and necrotic debris.

In case of *Candida* infection, the treatment with oral ketoconazole (200 mg a day) or fluconazole (150 mg single dose) is highly efficient.

If the patient complains of pain in the area treated, we should suspect of herpes, since the trigger for this infection at the lips or the vermilion area can be the trauma of a chemical exfoliation. According to Brody, the presence of pain is equal to a herpes infection, until proven otherwise. In this case, the infections will look like eroded areas without vesicles. Therapy is with acyclovir 400 mg, three times a day.

If we suspect of any infection, we should do a skin swab for culture and Gram coloration, to identify *Candida* and bacterial infections.

Other complications include:

- Milia (after 4–6 weeks)
- Itching
- Pore size increase
- Worsening of telangiectasia
- Acneiform eruptions
- Allergic reactions

A small group of patients will develop milia and present acneiform eruptions. They manifest as follicular, tender, multiple red papules, unlike the follicular pustules that might be seen during the healing process, because of the follicular occlusion caused by the excessive use of creams and ointments. There is a rapid improvement with the use of topical antibiotics, like clindamycin and erythromycin, or systemic antibiotics, like tetracycline, lymecyclin, or minocycline.

The allergic reactions to the chemical agents are rare and usually related to resorcinol.

Take Home Messages

- Chemical peels are easy to perform and very useful for the treatment of different dermatologic disorders.
- In order to start doing a chemical peel, we should know how to choose the best chemical agent to improve the specific dermatologic disorder.

– The ideal peeling is the one with a lower risk of complications and the higher benefit for the patient.
– It is very important to learn how to select the patient that can be a candidate for the peeling and to give him real expectations.

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Chemical Peelings: Body

Andréa Serra Rodrigues and Verena Miranda Cunha

Abstract

Chemical peels have always been the most economical therapeutic modality for skin rejuvenation and classified as superficial, medium, or deep based on their depth of penetration into the epidermis and dermis. Non-facial chemical peelings are best confined to light to medium peels because of the paucity of adnexal structures. These regimens of light to medium peels may yield significant improvement but must be performed conservatively and serially over time until results are satisfactory. The results are heavily dependent on concentration, contact time with the skin, and the manner of prepeel preparation. Deeper peels confer the risk of scarring, dyschromia, creation of a demarcation line between the treated and untreated area, and prolonged erythema.

Keywords

Non-facial Chemical Peelings • Photoaging, Acne, Post-inflammatory hyperpigmentation • Glycolic Acid, Trichloroacetic acid, Jessner's solution, Salicylic acid, Tretinoin

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Introduction

Chemical peeling represents accelerated exfoliation or skin damage induced by caustic agents that cause controlled damage, followed by the release

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of cytokines and inflammatory mediators, resulting in thickening of the epidermis, deposition of collagen, reorganization of structural elements, and increases in dermal volumes. This process decreases solar elastosis and replaces and reorients the new dermal connective tissue. The result is an improved clinical appearance of the skin, decreased pigmentary dyschromia, and a more youthful appearance.

Chemical peeling agents are classified as superficial, medium-depth, or deep peels. Superficial peels target the stratum corneum to the papillary dermis. They include glycolic acid, salicylic acid, Jessner's solution, tretinoin, and TCA in concentration of 10–30%. Medium-depth peels penetrate to the upper reticular dermis and include TCA in concentration of 30–50%, combination glycolic acid 70%/TCA 35%, Jessner's/TCA 35%, and phenol 88%. Deep chemical peels utilize the Baker-Gordon formula and penetrate to the midreticular dermis (Fischer et al. 2010; Flynn and Coleman 2000; Fulton and Porumb 2004; Monheit and Chastain 2001; Monheit 2004).

The depth is related to the results, i.e., the best results are reached with deep peels. However, the depth is also related with a longer time of reepithelialization and higher risks of complications.

Non-facial chemical peels should be, preferably, superficial peels and for better results, combined with another procedures and clinical treatments. Any extra facial region can be treated, but always reminding the reepithelialization is slower and harder due the less quantity of pilosebaceous units. A lot of agents and combinations can be used, but the results are not the same as in the face.

The most common agents used for non-facial chemical peels are Jessner's solution, trichloroacetic acid, alpha-hydroxy acids (such as glycolic, pyruvic, and mandelic acids), beta-hydroxy acids (such as salicylic acid and lipo-hydroxy acid), and tretinoin peeling.

New modalities of peelings, with different agents, concentrations, and combinations, have been reported, some of them with good results and, others, with unsatisfying results.

Complications after non-facial peels can occur and are more common if the right considerations are not taken. In general, they are similar as the complications observed after facial peels and should be treated in the same way, if occur. Cox described the development of multiple keratoacanthomas 2 weeks after a 70% glycolic acid gel and 40% chemical peel to the forearms (Cox 2003).

History

The perception of skin improvement with exfoliation is very old, with registry in Egyptian Ebers Papyrus, written in 1560 BC (Brody et al. 2000).

The Egyptians were the first civilization to use *peelings*. At that time, solar damage was considered a sign of inferior social position and women used a lot of different substances, such as alabaster, oils, salts, and baths with fermented milk (lactic acid), to improve the appearance of their skin.

The first report of medical use of chemical peeling was in 1882, from UNNA, a German dermatologist, who described the properties of salicylic acid, resorcinol, trichloroacetic acid (TCA), and phenol, which are used until nowadays (Brody et al. 2000; Fabbrocini et al. 2009). From then, many studies and publications have emerged about chemical peelings, especially in the last two decades.

In contrast to the others decades, chemical peels are now widely performed in darker racial-ethnic groups, individuals comprising skin types IV–VI (Asians, Hispanics, Blacks, and Native Americans) (Brody et al. 2000; Fabbrocini et al. 2009).

Indications

- Post-inflammatory hyperpigmentation
- Lentigines
- Superficial acne scars/superficial scars
- Post-acne pigmentation
- Comedonal acne
- Acne excoriée
- Acne vulgaris
- Photoaging
- Fine superficial wrinkling
- Seborrheic keratosis
- Actinic keratosis

- Pillar keratosis
- Buttocks' folliculitis
- Striae

Contraindications

Absolute contraindications include the following:

- Pregnancy
  - Active bacterial, viral, fungal, or herpetic infection
  - Open wounds
  - History of drugs with photosensitizing potential
  - Preexisting inflammatory dermatoses (e.g., psoriasis, atopic dermatitis, pemphigus)
  - Uncooperative patient (patient is careless about sun exposure or application of medicine)
  - Patient with unrealistic expectations

Other Considerations

Mental Health

Patients who are mentally unstable may not be prepared for their aesthetic appearance immediately following the peel.

Medications

A medical and drug history is very important.

Some medications may be photosensitizing and predispose patients to pigmentation complications after the chemical peeling and worsening the condition that the chemical peel was intend to treat.

Herpes Simplex

A history of herpes simplex requires antiviral prophylaxis from the immediate pre-peel until reepithelialization is complete (Drake et al. 1995). Acyclovir (400 mg) should be started 2 days prior to the peel and continued 5 days after the peel to reduce risks of recurrent herpes infection.

Some dermatologists advise prophylaxis in all patients to avoid the risks of a herpetic outbreak.

Any existing lesion must heal completely before any chemical peel.

History of Scarring

Patients must be asked if they have any history of hypertrophic scarring, because many people who have hypertrophic scarring can develop keloids. This fact is usually found in patients with Fitzpatrick skin types V and VI.

Weak superficial peels may be considered in patients with skin types V–VI because the penetration is only into the epidermis. Medium and deep peels penetrate into the superficial and deep dermis, which may stimulate keloidal development in patients who are inclined to develop keloids (Laundau 2008; Schurer and Wiest 2006; Bernstein 2002; Berson et al. 2009).

Follicle Unit Density

Patients who have had recent radiation treatment need to have a skin biopsy to be sure of the existence of hair follicle units, because these follicles are responsible for the reepithelialization.

Oral Isotretinoin

Previous use of isotretinoin must be noted, and patients must wait until 6 months after the last dose to reduce the risk of scarring.

Expectations

The physician and the patient may always discuss prior to a chemical peel. The possibility of

complications must be explained to the patient, and examples of before-and-after results should be shown.

Types of Non-facial Chemical Peelings

Glycolic Acid

It is an alpha-hydroxy acid, soluble in alcohol, derived from fruit and milk sugars. It is a natural product, known for its keratolytic property and for decreasing the cohesion between keratinocytes, causing desquamation. Furthermore, it's been demonstrated its capacity of stimulating keratinocytes and fibroblasts, improving extracellular dermal matrix (Okano et al. 2003; Corcuff et al. 2002).

It's present in a lot of cosmeceuticals products for acne, photodamaged skin, melasma, rosacea, and pseudofolliculitis barbae. Since the decade of 1990, it has been used as a superficial peeling agent, alone or combined with TCA 35% and 5-fluorouracil 5% (5-FU 5%). It's one of most common agents of the English literature, especially in the United States, where are available a lot of industrialized products with glycolic acid in different concentrations and with controlled pH (Corcuff et al. 2002).

In Brazil, it must be formulated, as we do not have it in the market. For this reason, unpredictable reactions as exaggerated frosting, epidermolysis, and unwanted hyperpigmentation after procedure can occur. Peeling solutions with a pH bellow 2 have demonstrated the potential to induce crusting and necrosis, which has not been seen with the partially neutralized solutions with a pH above 2. The more common concentrations are 20%, 30%, 50%, and 70%, and gel is the best vehicle, once it promotes slow penetration of the acid. The last concentration is widely used (Briden 2004; Brody 1997).

On non-facial areas, it can be used for photodamage, acne, and superficial acne scars, hyperpigmentation including black patients (Dinardo et al. 1996; Burns et al. 1997), fine wrinkles, lentigines, and multiple actinic keratosis (in this case, combined with TCA 35% or 5-FU 5%).

With the increasing use of nail art, nail paints, repeated manicures, cosmetic nail procedures, and detergents, the nail plate undergoes regular damage resulting in rough, lusterless, and pigmented nails. Banga and Patel (Cotellessa et al. 1999) used 70% glycolic acid for controlled keratolysis of the nail plate which can be a promising treatment modality for thick, uneven, rough, and pigmented nail plate conditions with cosmetically pleasing results.

Glycolic acid peels are contraindicated in contact dermatitis, pregnancy, and in patients with glycolate hypersensitivity.

Before applying glycolic acid, the skin is cleaned with alcohol, and the acid is applied with a large cotton applicator or with gloved fingers (Gurvinder and Kalpana 2014). Application time for weekly or monthly applications with 70% is generally 3 min (or less, as it's observed the beginning of frost or burning is reported), and the time is increased with subsequent peels. Neutralizers with 10% sodium bicarbonate have no advantage over water rising as long as all acid is well removed.

Following the peel, the skin is carefully observed for any complications, and the results are maintained with serial peels and by using at-home tretinoin or glycolic acid, besides sun avoidance (Jaishree 2013).

Jessner's Solution

This superficial peeling agent is a classic combination of 14% salicylic acid, 14% lactic acid, and 14% resorcinol in 95% ethanol. The great advantage of this formulation is the synergism of the three-keratolytic agents and the bleaching benefit of resorcinol (Tung 2000).

As a non-facial peeling, the best indications are for post-inflammatory hyperpigmentations and active acne, especially on trunk. It is also used to treat lentigines and photodamage.

Jessner's peeling is contraindicated during pregnancy, in patients with allergies to resorcinol, salicylic acid or lactic acid and hydroquinone hypersensitivity.

Before application, the skin is degreased with alcohol followed by acetone. In the authors' preference, Jessner's solution is applied with 2 × 2 folded gauze. Additional coats increase the depth of peeling and neutralization is not necessary. A whitish color on the skin surface immediately after the application must be distinguished from frost, and it is salicylic acid visible precipitation.

It is an excellent agent with a safety profile. It can be used in all skin types and enhances the penetration of TCA 35% and 5-FU.

Pyruvic Acid

It is an alpha-keto acid, a chemical group that has properties of both acids and ketones (Monheit 1989). It can be used for superficial, medium, or deep peelings, depending on the concentration of the application. Pyruvic acid at 100% or pure causes epidermolysis and collagen degeneration. It has been reported the use of 50% pyruvic acid solution for photoaging treatment and for active acne, with efficacy and safety and with minimal discomfort during application (Griffin et al. 1989; Cotellessa et al. 2004; Ghersetich et al. 2004). However, more studies are necessary to standardize its application, because it is still uncertain the way it acts and the level of its penetration.

Resorcinol

It is related to phenol both structurally and chemically. In 1882, Unna described the use of resorcinol in chemical peels in concentrations of 10, 20, and 30% (Griffin and Van Scott 1991), but later the formula was modified to obtain a 50% concentration (Unna 1882). Resorcinol is soluble in water, ether, and alcohol and has keratolytic properties.

It is considered a superficial peeling and is indicated for acne, post-inflammatory hyperpigmentation, and photoaging.

Contraindications are skin type more than V, allergic reaction to resorcinol, pregnancy, and infections in general.

Previous test is necessary.

The patient must be at the supine position to prevent syncope, and the paste is spread over the area with a tongue depressor or gloved finger and kept from 1 to 2 h. The patient complains a burning sensation.

Depending on the concentrations, complications can be transitory hyperpigmentation and dizziness (probably due the flushing).

Trichloroacetic Acid

TCA occurs naturally as a colorless crystal and is easily formulated by mixture with distilled water. It is a chemical cauterizing, when applied to the skin causes protein denaturation and cellular necrosis, resulting in a readily observed white frost (Karam 1993). It is an inexpensive solution that can be easily prepared, is stable, has a long shelf life (at least 2 years), and does not have any systemic toxicity. The degree of skin penetration and injury depend on several factors, including strength of TCA used, skin preparation, numbers of coats applied, and anatomic site (Vossen et al. 2000). The common concentrations are 10%, 20%, 35%, 40%, and 50%. It can be combined to other agents, especially to Jessner's solution and glycolic acid (Collins 1989).

On non-facial areas should be used up to 30% concentrations and always trying to achieve erythema with blotchy or wispy areas of white frosting. This indicates a superficial epidermal peel. The results are very satisfying for the treatment of photoaging with keratosis (non-hypertrophic) and solar lentigo (Monheit 2001).

A study comparing the results of combined 70% glycolic acid/35% TCA with cryosurgery for the treatment of solar lentigo (Chun et al. 2004) on the hands revealed both treatments have same efficacy; however, the combined peel was superior in terms of less pain and side effects (focal hypopigmentation).

After defatting the skin, it is applied with folded 2 × 2 gauze and neutralization is not necessary. It does not need to be removed.

Chemical peel of non-facial skin using 70% glycolic acid and 35–45% TCA over it (Cook's

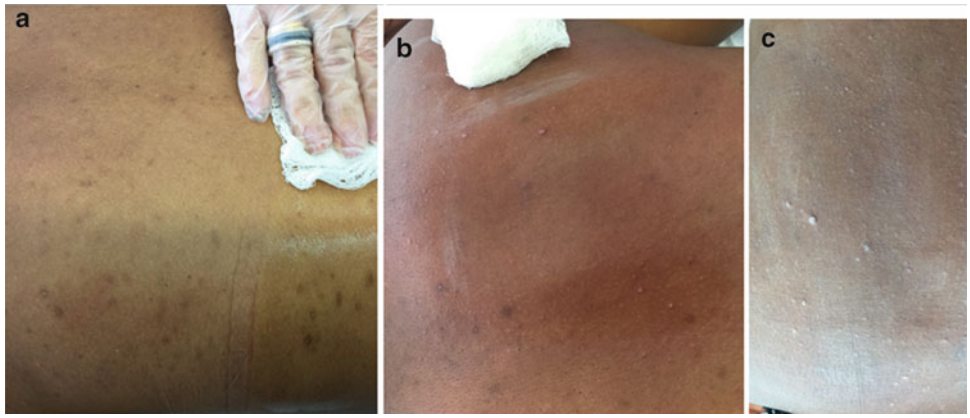

Fig. 1 **a** Applying salycilic acid on trunk with gaze. **b** Salycilic acid precipitation can be observed after some minutes. **c** *Whitish* color after 5 min (salycilic acid crystallization)

body peel) (Sezer et al. 2007; Cook and Wr 2000) has also been reported to be successful for rejuvenation of the hand (Cook-Bolden et al. 2005). The glycolic gel acts as a partial barrier, limiting the penetration of the TCA. After 2–4 weeks of light white flaking, smooth texture with less wrinkling and fading of lentigines have been reported. Cook's body peel is a very good option to also treat the neck and chest (Slavin 2000) but requires experience and constant observation to be immediately neutralized, because deeper peels confer the risk of scarring and dyschromia.

TCA is one of the most rewarding procedures in the treatment of many conditions, ranging from pigmentary disorders to moderate photoaging, when performed properly. It should be done with care for body areas.

Salicylic Acid

It is the ortho-hydroxybenzoic acid, a beta hydroxy acid agent. It is a lipophilic compound that removes intercellular lipids that are covalently linked to the cornified envelope surrounding cornified epithelioid cells (Jasin 2000). In concentrations of 3–6%, it is keratolytic and comedolytic (Lazo et al. 1995) and for these reasons is frequently utilized in topical acne preparations. In addition, it also enhances penetration of other topical agents.

As a superficial peeling agent for non-facial areas is utilized, concentration of 30% in ethanol and the indications include acne vulgaris (inflammatory and non-inflammatory lesions), melasma, post-inflammatory hyperpigmentation, lentigines, and mild to moderate photodamage. It is performed at 2- to 4-week intervals, and the results are achieved with a series of three to six peels.

After defatting the skin, the acid is applied with folded 2 × 2 gauze (authors' preference) in a total of two to three coats. A white precipitate represents crystallization of the salicylic acid (Fig. 1a–c), and this should not be confused with frosting, which represents protein agglutination.

Grimes et al. reported substantial efficacy and minimal side effects in 25 patients treated with 20 and 30% salicylic acid peels in darker-ethnic groups, including melasma, acne vulgaris, and post-inflammatory hyperpigmentation (Imayama et al. 2000; Grimes 1999; Tosti et al. 2012).

A Korean study, with 35 patients treated for facial acne with salicylic acid 30% biweekly for 12 weeks, demonstrated improvement for both inflammatory and non-inflammatory lesions. In general, the peel was well tolerated with few side effects (Uhoda et al. 2003; Roberts 2004).

Given these findings, salicylic acid peels are well tolerated in all skin types (Fitzpatrick's I–VI) and all racial/ethnic groups.

It is reported the risk of salicylism (salicylic acid toxicity) (Lee and Kim 2003), which is

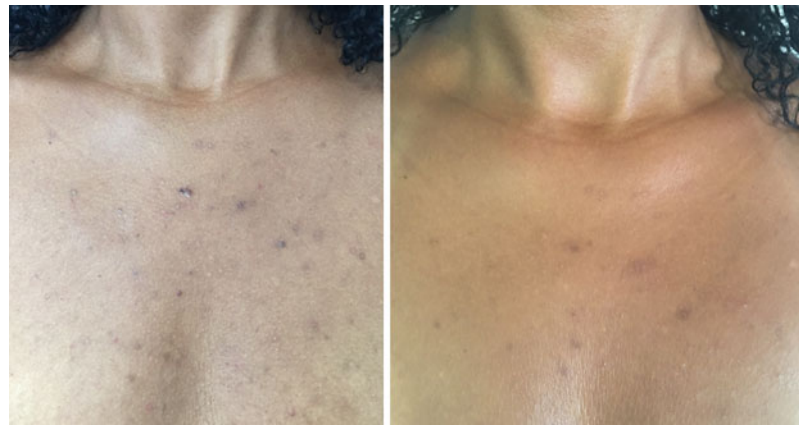

Fig. 2 Before and after (trunk-chest) one session of salycilic acid for acne lesions and postinflammatory hyperpigmentation in a patient Phototype VI

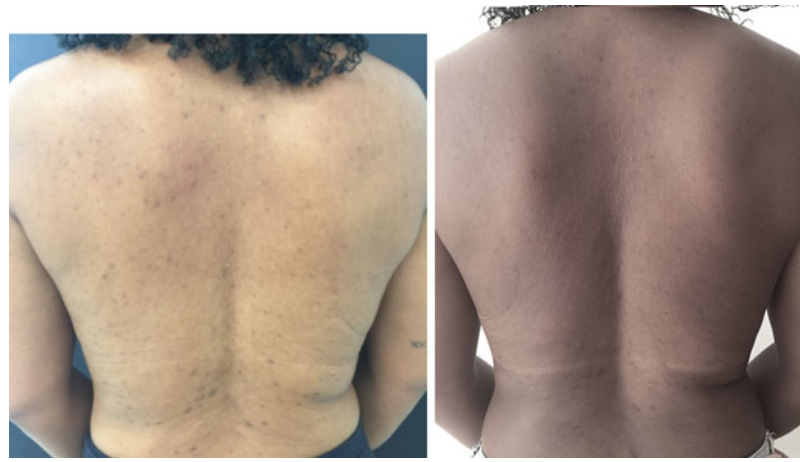

Fig. 3 Before and after (trunk-dorsum) one session of salycilic acid for acne lesions and postinflammatory hyperpigmentation in a patient Phototype VI

characterized by rapid breathing, tinnitus, hearing loss, dizziness, abdominal cramps, and central nervous system reactions. It has been reported with 20% salicylic acid applied to 50% of the body surface. It is not a common reaction at all. Salicylic acid peels are current in our practice, and we never observed one single case of salicylism (Figs. 2, 3).

LHA

It is derived from salicylic acid called beta-lipohidroxy acid, used in concentrations above 10%. It is comedolytic and, once it is more lipophilic than salicylic acid, has a good penetration in pilosebaceous unit and epidermis. The pH is similar to the normal skin (pH = 5.5), so it is very tolerable and neutralization is not necessary.

The studies revealed significant reduction of the number and size of microcomedones and bacteria in the follicle, with no side effects.

Salicylic-Mandelic Peels (SMP)

Mandelic acid is obtained from almond extract, and its molecule is bigger than the one of glycolic acid. For this reason, it penetrates less into the skin. The pH is acid.

At concentrations of 5%, it decreases the cohesion between keratinocytes. The indications are

the same for glycolic acid, but for sensitive skins, once it appears to be more safety.

The SMP (Cassano et al. 1999) is an association, and at the same formulation, of mandelic acid (10%) with salicylic acid (20%), for the treatment of acne and post-inflammatory hyperpigmentation, very useful on the chest and trunk.

Fluor-Hydroxy Pulse Peel

5-FU is an antimetabolite and has similar chemical structure to the pyrimidine molecules of DNA and RNA. Because of that, it acts as a cytotoxic drug against cells with DNA mutations and inhibits DNA and RNA synthesis, destroying hyperproliferative precancerous lesions.

It is a classic substance used for the treatment of multiple actinic keratosis (Garg et al. 2009; Bagatin et al. 2009), as a cream, twice a day, during 2–4 weeks.

The *fluor-hydroxy pulse peel* (Bagatin 2010; Katz 1995) is a 5-FU 5% solution in propilenoglycol applied with gloved fingers and combined to previous application of Jessner's solution or 70% glycolic acid. The solutions are applied weekly for an 8-week period. This regimen not only provided cosmetic improvement but also has a therapeutic effect on premalignant lesions without the usual morbidity (side effects) related to 5-FU regular therapy.

It is indicated for advanced photoaging with multiple actinic keratosis and actinic porokeratosis. (Marrero and Katz 1998)

Tretinoin

Tretinoin or all-trans-retinoic acid, also called retinoic acid, is indicated for treatment of melasma, acne vulgaris, photoaging follicular keratosis, striae, and disorders of keratinization. (Teixeira et al. 2005)

The continuous use of 0.025%, 0.05%, or 0.1% tretinoin cream is considered part of a gold standard treatment for photoaging (Cucé et al. 2001).

The first proposal about the use of higher concentrations of tretinoin as an agent for superficial peeling was reported by a Brazilian group in 2001 (Griffiths et al. 1993). The authors used 1%, 2%, 3%, 4%, and 5% tretinoin concentrations, sequentially, in a solution with equal parts of ethanol and propilenoglycol, in five sessions, two applications per week and reported no discomfort. The remaining solution should be washed out after 6–12 h, at home. One year later, they recommend 5% tretinoin peeling, once a week, in three applications. The results were satisfying for melasma, acne, and photoaging in any region of the body, but with few considerations about skin penetration.

A study comparing different tretinoin concentrations (0.25%, 1%, and 5%) and two vehicles (cream and hydroalcoholic dispersion) was aimed to evaluate the influence of drug concentration and vehicles currently used on skin penetration of tretinoin. Permeation and retention in vitro tests were carried out using Franz diffusion cells, and tretinoin concentration in skin layers was determined by high-performance liquid chromatography. The largest amount of tretinoin from both vehicles was detected in stratum corneum, and the hydroalcoholic dispersion was the best vehicle. The formulation with 0.25% tretinoin showed better results when considered the amount of tretinoin on skin in terms of percentage. This study highlights that 0.25% tretinoin cream formulation showed high cost-to-benefit ratio mainly when compared to the cream formulations with four (1%) and twenty (5%) times of this active ingredient. (Bagatin et al. 2011)

More comparative studies are necessary between daily use of tretinoin and series of superficial chemical peelings with tretinoin to demonstrate or not advantages of these procedures.

Final Considerations

Non-facial chemical peelings agents are inexpensive and safe, but a proper understanding of the correct techniques, indications, limitations, and complications is paramount before using them (Kligman and Draelos 2004; Rendon et al. 2010; Zakopoulou and Kontochristopoulos 2006).

A lot of agents and combinations can be utilized, but as a rule non-facial skin takes much longer to heal and is at much greater risk of scarring than when using a similar concentration on the face. This is due the paucity of adnexal structures on non-facial regions, and it always has to be considered.

Beyond the poor wound healing and higher risk of scarring, another major limitation of chemical peeling off the face is lack of efficacy in comparison with the face.

Multiple superficial chemical peels generally do not equal the efficacy of a single medium-depth peel, which is contraindicated on non-facial skin.

Life style, psychological profile of the patient, and realistic expectations about the peelings are very important to be determined, in order to minimize risk of complications.

Use of sunscreens, bleaching agents, and tretinoin can reduce pigmentary changes, which can develop post-peeling (Wiest 2004). Actually, the complications are the same as in the face, except with a higher risk for the reasons once exposed.

Take Home Messages

- Non-facial chemical peelings are very useful for a lot of conditions, when well executed.
- Dermatologists may domain the technique of chemical peels.
- It is important to understand the limitation of the procedure for non-facial areas in order to avoid unnecessary side effects.
- Some chemical peels can be combined to improve the results.
- Superficial peelings, but not medium peeling, are indicated for non-facial areas.

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Physical Procedures

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Abstract

This chapter aims to explore the most commonly used physical procedures in dermatology's daily practice: electrosurgery and cryosurgery. Cryosurgery is an effective and efficient method for benign, premalignant, and malignant cutaneous lesions. It evolves cell destruction by the application of very low temperatures. Electrosurgery is a physical method used to destroy benign and malignant lesions, to control bleeding, and to cut and excise tissue. It causes denaturation of cellular proteins, resulting in coagulation and desiccation effects. Their origins, principles, and mechanisms of action will be explained, as well as indications, advantages, and risks of each technique will be concerned.

Keywords

Electrosurgery • Cryosurgery • Physical procedures • Benign lesions • Premalignant lesions • Malignant lesions

Contents

Introduction

Cryosurgery is a common treatment modality used as an effective and efficient method for benign, premalignant, and malignant cutaneous lesions (Zouboulis 1998). It evolves cell destruction by the application of very low temperatures to living tissues, being well tolerated and producing good cosmetic results (McIntrye et al. 2007). Cryosurgery is specially favored in patients who cannot tolerate excisional surgery (individuals on anticoagulants), those allergic to local anesthetics, elderly patients with comorbidities, and pregnant women (Zouboulis 1999). Cryosurgery can be easily performed in the office setting, preparation time is short, and treatment requires no expensive supplies or injectable anesthesia. The risk of infection

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is low, wound care is minimal, and suture removal is not needed (Guidelines of care for cryosurgery 1994) (see chapter "Cryotherapy for Cosmetic Procedures" – Vol. 2).

Electrosurgery is a physical method used to destroy benign and malignant lesions, to control bleeding, and to cut and excise tissue (Usatine 1998). It is based on the fact that electrical energy can be converted into molecular energy, which causes denaturation of cellular proteins, resulting in coagulation and desiccation effects (Hainer 1991). Electrosurgery is suitable for the everyday office practice, is not time-consuming, and has acceptable to excellent results (Sebben 2000) (see chapter "Electrosurgery for Cosmetic Procedures" – Vol. 2).

History

J. Arnott (1851) firstly used extreme cold locally to destroy tissues. He used a mixture of chloride of sodium and crushed ice for palliation of tumors, with resultant reduction of pain and local hemorrhage. He stated that "a very low temperature would arrest every inflammation which is near enough to the surface to be accessible to its influence" (Arnott 1851). Aiming palliation, Arnott treated breast cancer, uterine cancers, and some skin cancers. Nevertheless, he recognized the potential of cold for curing cancer. He also advocated cold treatment for acne, neuralgia, and headaches, achieving temperatures of −24 °C. In addition, he recognized the analgesic "benumbing" effect of cold, recommending the use of cold to anesthetize skin before operation. He was concerned about the safety of the new anesthetic agents that were being introduced and advocated the use of cold as an alternative (Arnott 1851).

Allington is thought to have been the first to use liquid nitrogen, in 1950 (Allington 1950). After the Second World War, liquid nitrogen became freely available and was preferable to liquid oxygen with its explosive potential. He used a cotton swab for treating various benign lesions, but poor heat transfer between swab and skin meant this method was insufficient for tumor treatment (Allington 1950).

The use of cryosurgery was facilitated by the development of devices more suitable for office-based practice. Torre developed a liquid nitrogen spray in 1965, and Zacarian a handheld device, the Kryospray, in 1967 (Zacarian 1985). Zacarian's spray allowed one-handed operation with trigger type control, and interchangeable tips permitted variations in spray diameter. Zacarian also developed copper probes that allowed tissue freezing to depths of up to 7 mm. His contributions to cryosurgery equipment, understanding of the science of the cryolesion and the published work on cryosurgery was very great (Kuflik 1990; Cooper and Dawber 2001).

In old history, the hot cautery was used by Egyptians and Greeks to stop bleedings, to wound heals, and to treat abscesses and tumors. The use of electricity to generate heat started in 1875, when Paquelin developed the electrocautery (Fewkes et al. 1992).

Electrophysics experiments in the nineteenth century led to the understanding of the principles of what would later become electrosurgery. Arsene d' Arsonval applied high frequency electric currents (10,000 hertz) in humans in 1891, and demonstrated they could pass through the body without neuromuscular stimulation or tetanic response (D'Arsonval 1891; D'Arsonval 1893). In 1900, Riviere reported the treatment of an ulcer (probably a squamous cell carcinoma) on the dorsum of a musician's hand using high frequency sparks (Pollack et al. 2000). In 1907, Walter de Keating-Hart and Pozzi described the term "fulguration" for the resulting carbonization when Oudin's spray of sparks was used to treat skin cancer, claiming that the spark could selectively destroy tumor cells (Pollack et al. 2000). In 1909, Doyen described "electrocoagulation" as a different form of electrosurgery, in which the electrode touched directly the tissue, and an indifferent electrode was added to the circuit. It caused the electricity to flow back to the surgical device, recycling energy, what allowed low voltages to be used, with high amperages. This biterminal arrangement penetrated deeper than fulguration, and was claimed to be more effective in destroying tumor cells, not only causing carbonization of the

surface but also coagulating tissues directly (Pollack et al. 2000). In 1911, Clark used a smoother current that produced finer sparks, rather than the thick sparks of electrofulguration, and used the term "dessication" to describe the dehydration of tissue without carbonization of the surface (Pollack et al. 2000). Wyeth was the first to use, in 1923, an apparatus based on electrosurgery for cutting tissues, which he termed "endotherm knife," and the technique "electrothermic endothermy." He was a noted tumor surgeon, and claimed that the technique sealed off small vessels and also the lymphatics, reducing metastatic dissemination (Pollack et al. 2000).

William Bovie developed an electrosurgical device that offered both coagulation and cutting currents, probably one of the most important developments for electrosurgery. The device was broadly used to stop bleeding and cutting by Harvey Cushing, a distinguished neurosurgeon, whose positive impressions raised the acceptance of electrosurgery in medicine (Pollack et al. 2000).

Mechanisms of Action

Cryosurgery promotes the destruction of lesions through mechanisms that include impairment of homeostatic functions, tissue damage, blood stasis, occlusion, and inflammation (immunologic effect, not fully understood) (Moioli and Krunic 2014). Ice crystal formation due to freezing water outside and inside the cell promotes dehydration and physical cell damage, causing vasoconstriction, vascular stasis, anoxia, and necrosis (Thai and Sinclair 1999).

According to the temperatures reached, cryosurgery induces selective destruction of different cell or tissue types. Connective tissues are more resistant to cryo-damage than the epidermal cell types (especially melanocytes and deeper epidermis). Fibroblasts and collagen are very resistant to cold, what is blamed to cause the difficulty in treating keloids with cryosurgery. Malignant lesions need lower temperatures to be destroyed, and benign lesions can be treated more superficially (Gage 1979).

Electrosurgical devices transfer electrical energy to human tissue through an electrode, which remains cool. Human tissue's electrical resistance helps converting electrical energy into molecular energy, leading to denaturation of intra- and extracellular proteins, with coagulation or dessication effects. Intracellular water's temperature rises above boiling point, causing disrupture of cell membranes, with cutting effect (Hainer 1991; Hainer and Usatine 2002). In biterminal electrosurgery, the patient is part of the circuit, connected to the apparatus by a dispersive electrode. In monoterminal devices, the patient is not included in the circuit (Blankenship 1979).

Modalities

Among several cryosurgery techniques available, the most suitable must be chosen according to the lesion characteristics and personal preferences. The open spray technique is the most commonly used. Other techniques include the traditional dipstick technique, carbon dioxide technique, confined spray, metal chamber, cryoprobe, cryo tweezers, and intralesional cryosurgery (Kuflik and Kuflik 2012; Pasquali and Sebastian 2010).

The major modalities in electrosurgery are electrodessication, fulguration, electrocoagulation, and electrosection. In electrodessication, the electrode touches the skin to produce tissue destruction. In fulguration, the electrode is held away from the skin and produces sparking on the surface, leading to more superficial tissue destruction. In electrocoagulation, the electrode tip is used for clotting small blood vessels, directly on surgical bed or indirectly touching a hemostat. In electrosection, the electrode is used to cut tissue, with minimal heat damage along the margins. Blended, or "cut and coag" currents enable to perform nearly bloodless surgery, with excellent cutting ability and coagulation capacity (Hainer and Usatine 2002).

Electrocautery is an old-fashioned technique in which the electrode, rather than human tissue, serves as electrical resistance: the electrode tip rises temperature and causes burn in tissues (Hainer and Usatine 2002).

Indications

Cryosurgery

Cryosurgery achieves various success rates and side effects, depending on factors that affect specific lesion responses (Afsar et al. 2015). Even if prior biopsies can prove the malignant or benign characteristics of a lesion, cryosurgery fails to provide the precise histological evidence of complete tumor removal, comparing it to excisional procedure. Furthermore, the results in cryosurgery are not immediate, as provided by more destructive techniques (Abramovits et al. 2002).

Sun damaged skin and sun-induced neoplasms are amenable to be treated with cryosurgery: solar lentigines, solar keratoses, colloid millium, sebaceous hyperplasia, pigmented skin, and fine wrinkles respond to cryosurgery. Some lesions respond to a single treatment, while others need several sessions (Afsar et al. 2015).

Benign Lesions

- Common warts: Cryosurgery is recommended as first-line therapy for flat and common warts. The weekly treatment clears warts faster than treating them every 2 or 3 weeks, but the overall success depends on the total number of treatments, size of warts, and degree of hyperkeratosis (Afsar et al. 2015; Gibbs et al. 2003).
- Anogenital warts: Cryosurgery is effective in treatment of condiloma accuminatum, particularly when podophylin treatment failed, or is not indicated (pregnancy, undesirable areas). Shorter freeze times are required in areas where the dermis is thinner, like on the penile shaft, to avoid damaging structures.
- Callosity: Cryosurgery can be used with or without pretreatment with keratolytics (Afsar et al. 2015) (See "Ablative Lasers (CO_2 Laser) for Other Indications" – volume 3).
- Molluscum contagiosum: The lesion can be lightly frozen until it turns white, and then removed with a small curette, with unusual scarring (Lubritz 1985).
- Seborrheic keratosis: Cryosurgery is especially effective in patients with multiple lesions, associated to shave excision or curettage. The potential hair loss on treated areas must be considered, and also hypopigmentation and atrophic scar (Afsar et al. 2015) (see "Ablative Lasers (CO_2 Laser) for Other Indications" – Vol. 3).
- Keloid scar: Cryosurgery can be used either in monotherapy or associated to intralesional triamcinolone. Due to fibroblasts resistance to cold, best responses are seen with three or more consecutive treatments, repeated every 20–30 days (Pasquali et al. 2016; Zoubolis et al. 1993).
- Vascular lesions: Capillary hemangiomas of the newborn can have excellent response to contact cryosurgery, whereas cavernous and capillary hemangiomas of the adult are more difficult to treat, because of their size and depth (Zouboulis 1998; Afsar et al. 2015). Pyogenic granuloma can be alternatively treated with cryosurgery, although the choice treatment is surgical excision (Afsar et al. 2015) (see "Laser Treatment of Vascular Lesions" – Vol. 3).
- Leishmaniosis: It has been demonstrated that three sessions of cotton-tipped applied liquid nitrogen can have results comparable to antimonials (Afsar et al. 2015; al-Majali et al. 1997).
- Ingrown nails: Cryosurgery can achieve results comparable to other surgical nail sparing procedures, being easier to perform and producing rapid relief of pain, without needing anesthesia (Afsar et al. 2015) (see "▶ Cosmetic Approach for Healthy and Damaged Nails" – Vol. 1).
- Prurigo nodularis: Although residual scarring may occur, and it takes long time (up to 4 weeks) for the nodules to heal, cryosurgery is a widely used option for this condition (Afsar et al. 2015).
- Solar lentigines: Superficial cryotherapy can be performed in lentiginous lesions. Hyperpigmentation can occur. Biopsies must be performed before treatment, if there is any sign of malignancy, to reassure it is not lentigo maligna/melanoma (Guidelines of care for cryosurgery 1994; Afsar et al. 2015) (see "Intense Pulsed Light for Photorejuvenation").
- Other conditions include acne cysts, acrochordons, angiofibromas, cherry and spider

angiomas, chondrodermatitis nodularis helicis, lichen planus-like keratosis, dermatofibroma, granuloma annulare, granuloma faciale, gutatte leucoderma, lymphangiomas, nipple adenoma, porokeratosis, rosacea, sebaceous hyperplasia, steatocystoma multiplex, syringoma, venous lake, verrucous epidermal nevi, and xanthelasma (Afsar et al. 2015; Kumarashinghe 2004; Pasquali et al. 2016; Mlacker et al. 2016; Labandeira et al. 2015) (see "Ablative Lasers (CO_2 Laser) for Other Indications" – Vol. 3; "Laser for Vascular Lesions" – Vol. 3).

Premalignant Lesions

- Actinic keratosis: Cryosurgery has high cure rates reported. It is more efficient in thin, well-demarcated lesions, or small number of scattered lesions (see "▶ Photodynamic Therapy" – Vol. 1). One session is usually enough, but long-term recurrences are common. Biopsies should be taken in thick rapid growth lesions, to rule out squamous cell carcinoma, and pigmented lesions in melanoma suspicion (Afsar et al. 2015). Actinic cheilitis and Bowen's disease can also be treated with cryosurgery, always awaking of malignant transformation.

Malignant Lesions

- Cryosurgery is also suitable to tumors with circumscribed well-demarcated borders, such as low-risk basal cell carcinomas, squamous cell carcinomas, Kaposi's sarcomas, and nonoperable disseminated cutaneous metastases of malignant melanoma (Zouboulis 1998; Afsar et al. 2015) (see "▶ Photodynamic Therapy" – Vol. 1).

Electrosurgery

Injectable lidocaine is administered before most electrosurgical techniques, and the use of epinephrine reduces blood loss (the use should be avoided at the digits and nose). Otherwise, anesthesia may not be necessary for small lesions like skin tags or small telangiectasias (Hainer and Usatine 2002).

Electrosurgery has many applications in cutaneous surgery. Incisional techniques produce full-thickness excision of nevi; shave-techniques produce partial-thicknesses removal of superficial lesions like warts; vascular lesions such as pyogenic granulomas can be removed with minimal blood loss.

- Indications range from benign conditions (like acrochordons, cherry and spider angiomas, condyloma acuminatum, hydrocistoma, millium, molluscum contagiosum, nevi, pyogenic granuloma, seborrheic keratosis, sebaceous hyperplasia syringoma, telangiectasias, rhinophyma, rosacea, verrucae vulgaris and verrucae plana, xantelasma) to premalignant lesions (actinic keratosis), and malignancies (basal cell carcinoma) (Sebben 2000; Hainer and Usatine 2002; Hofmann and Lehmann 2016) (see "Ablative Lasers (CO_2 Laser) for Other Indications" – Vol. 3).
- Cherry angiomas: Electrosurgery is the most effective and inexpensive treatment. Larger lesions can be shaved first, and then coagulated or desiccated at the base. Smaller lesions can be lightly electrocoagulated.
- Pyogenic granuloma: Those benign vascular tumors are ideally treated with electrosurgery. The elevated part can be shaved off and sent for pathology (to rule out amelanotic melanoma), and the base of the lesion should be scraped with a sharp curette and electrocoagulated.
- Basal cell carcinoma: After local anesthesia, the lesion should be scraped with a sharp curette in all directions and borders, and next the base should be fulgurated or desiccated, respecting adequate tumoral margins. Another approach is the full-thickness elliptical excision via electrosection, with reduced appreciable bleeding (Hainer and Usatine 2002) (see "▶ Photodynamic Therapy' – Vol. 1).

Side Effects

Potential adverse effects of cryosurgery include hypo- or hyperpigmentation, infection, scarring, and hair loss. Serious reactions are rare. Patients

should be warned that secondary effects like erythema, exsudation, edema, pain, and vesicles can be expected. Contraindications are usually related to comorbidities such as cryoglobulinemia, Raynaud's disease, blood dyscrasias, cold intolerance, cold urticaria, pyoderma gangrenosum, and autoimmune disease (Thai and Sinclair 1999; Pasquali and Sebastian 2010; Afsar et al. 2015). Cryosurgery in lesions located in hairy scalp, eyebrows, and the central part of the face pose an increased risk for scarring alopecia; also there is a higher risk of ulceration in the lower legs and feet, due to poor vascularization (Afsar et al. 2015).

In electrosurgery, complications such as burns, shocks, viral, and bacterial transmission can be prevented using carefully the electrosurgical equipment following recommendations, including strict electrode sterilization, careful and close smoke plume evacuation (Hainer and Usatine 2002).

Contraindications include the use of cardiac pacemaker and treatment of melanoma. Electrosurgery has the potential for interfering with pacemaker function, delivering alternating current to the heart, resulting in ventricular fibrillation. Despite the fact that most modern pacemakers are well shielded from external radiation, alternative treatment methods should be used in these patients. The guidelines for using electrosurgery in those patients include avoidance of this modality in unstable cardiac patients, and the delivery of several short bursts of energy rather than a long one (Sebben 1983). In patients with implantable cardioverter-defibrillators (ICD), cardiologist should be consulted for possible inactivation of ICD prior to surgery (Levasseur et al. 1998).

Take Home Messages

- Cryosurgery promotes the destruction of lesions through mechanisms that include impairment of homeostatic functions, tissue damage, blood stasis, occlusion, and inflammation.
- According to the temperatures reached, cryosurgery induces selective destruction of different cell or tissue types.
- Connective tissues are more resistant to cryodamage than the epidermal cell types (especially melanocytes and deeper epidermis).
- Malignant lesions need lower temperatures to be destroyed, and benign lesions can be treated more superficially.
- Electrosurgery is based on the fact that electrical energy can be converted into molecular energy, which causes denaturation of cellular proteins, resulting in coagulation and desiccation effects.
- Solar lentigines, solar keratoses, colloid millium, sebaceous hyperplasia, pigmented skin, and fine wrinkles respond to cryosurgery.
- Acrochordons, cherry and spider angiomas, seborrheic keratosis, sebaceous hyperplasia, syringoma, telangiectasias, rhinophyma, xantelasma), and actinic keratosis can be treated with electrosurgery.

Cross-References

▶ Approach in Photodamaged Skin, Melasma, Acne, and Rosacea

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Lasers, Lights, and Related Technologies in Cosmetic Dermatology

Alvaro Boechat, Luis Torezan, and Nuno Osório

Abstract

Lasers have been widely used in dermatology for almost 50 years. Selective targeting of the skin chromophores allowed practitioners to treat many skin conditions which were difficult or had no available treatment until introduction of selective photothermolysis in the early 1980s.

The demand for laser surgery has increased substantially in the past few years. Refinements in laser technology have provided patients and dermatologists with more therapeutic choices and improved clinical results. Innovations have allowed the range of conditions and the skin types suitable to treatment, including vascular and pigmented lesions, scars, tattoos, improvement of photoaging, and hair removal. More recently, fractionated laser devices were developed which contributed to higher efficacy and safety especially for higher skin types.

In this chapter, we present the basic concepts of lasers and tissue optics and also the different laser types, which are classified according to their tissue target and tissue interactions, such as vascular, pigment, photoepilation, and resurfacing lasers. Non-laser technologies, such as intense pulsed light, radio frequency, ultrasound, and cryolipolysis, are also discussed.

Keywords

Laser • Radio frequency • Photothermolysis • Intense pulsed light • Tissue interaction • Wavelength • Ultrasound • Light amplification • Fluence • Stimulated emission

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Contents

Introduction

Laser and pulsed light are simply sources of natural light. The visible light that we experience in our day to day is only one facet of a much broader physical phenomenon known as "electromagnetic radiation."

As shown in Fig. 1, the electromagnetic spectrum (Siegman 1986) includes several well-known phenomena, such as TV and radio waves, microwave, infrared, and, on the other side of the spectrum, ultraviolet and X-ray. However, our eyes are sensitive to only a very narrow range of the spectrum, which forms the visible light from violet to red. It is important to realize that each visible color or each emission spectrum is associated with a frequency or wavelength.

Thus, the differentiation between blue and green, for example, is related to their frequencies. It is similar to the musical notes; the difference of the note "do" (C) from the note "sol" (G) or "fa" (F) is their frequencies; one is low pitched and the other high pitched. Drawing a parallel with them, we can see that, in the light spectrum, the higher frequencies correspond to blue and violet and, on the other side of the spectrum, the lower frequencies correspond to red. As light frequencies are very high, of the order of millions of hertz, they are characterized by their wavelength, or the distance between two adjacent peaks in the wave illustrated in Fig. 2 (Siegman 1986; Arndt et al. 1997).

Light radiation may be defined as the point-to-point power transmission in space, regardless of the medium in which it is being propagated. Light or electromagnetic radiation propagates at a high speed in the open space independent of the transmission medium in the form of waves that can travel in the vacuum or in spaces containing matter, such as gases, liquids, or solids. As it enters, or moves from, a different medium, it will suffer changes in direction and speed of propagation.

Lasers are sources of electromagnetic radiation, or light, with some special characteristics that are different from other light sources, such as a car headlight or a lamp.

The word **laser** is an acronym for **light amplification by stimulated emission of radiation**. We can divide this acronym into two well-defined parts: the stimulated emission phenomenon and the light amplification.

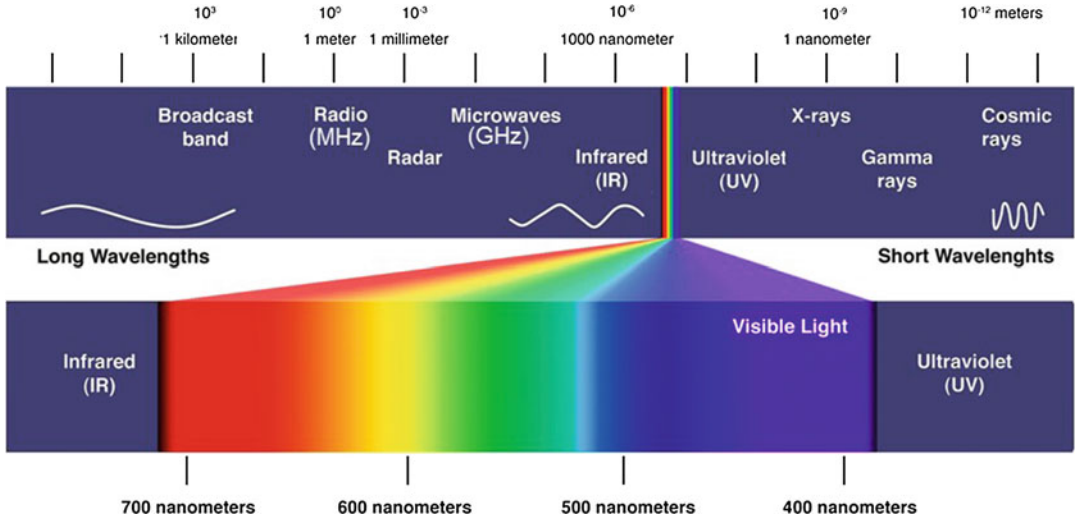

Fig. 1 The electromagnetic spectrum

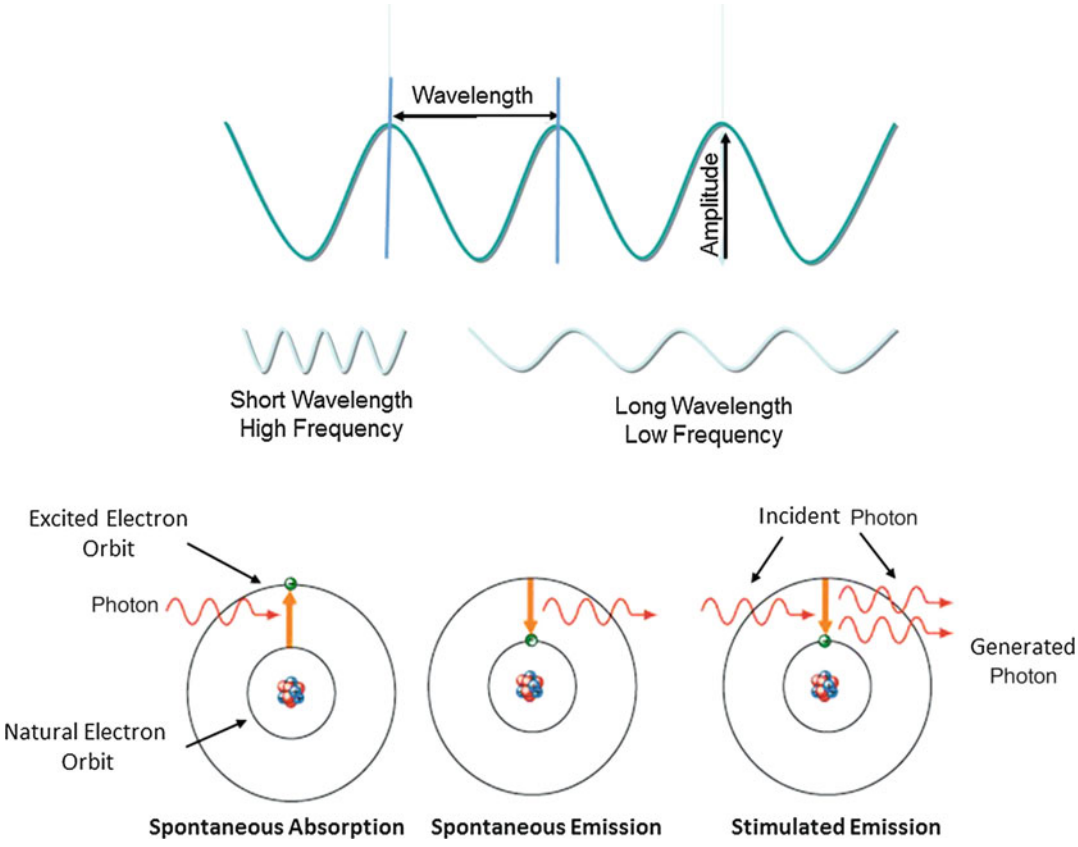

Fig. 2 Electromagnetic waves of photons that transport energy

Stimulated Emission

Light is a form of energy generated, emitted or absorbed by atoms or molecules. To emit energy, the atom or molecule is raised to an excitation energy level, above its natural resting state (in which there is excess energy to be discharged). Atoms cannot maintain the excitement for long periods of time. Consequently, they have a natural tendency to eliminate the excess energy in the form of emission of particles or packets of light waves called photons (Fig. 3a). This phenomenon is called spontaneous emission of light. The wavelength (λ), or the frequency of the emitted photons, is related to the photon energy through the relationship:

$$E_{photon} = hc/\lambda$$

h – Planck universal constant = 6.6260693 $\times 10^{-34}$ J.s
c – Speed of light = 300,000 km/s
λ – Wavelength of the light (nanometers – nm)

Each atom or molecule in nature has different energy levels of excitement. Consequently, each element emits photons with different energies and different wavelengths (frequencies). All these primary radiations are monochromatic. The fact that the sunlight is polychromatic indicates that it is composed of a mixture of several distinct elements.

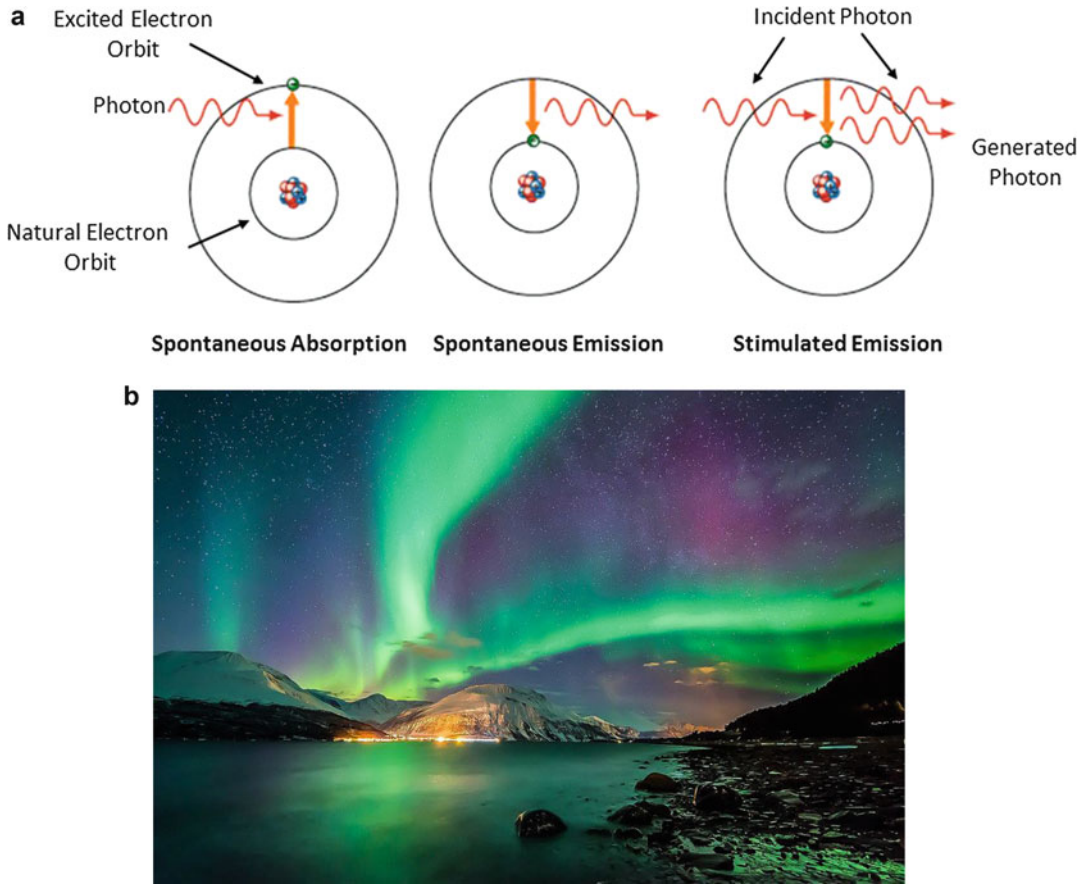

Fig. 3 (**a**) Spontaneous emission of light. (**b**) Northern Lights, or *aurora borealis*, example of spontaneous emission of light

Atoms can be excited by different mechanisms: heat, mechanical shocks with other particles as an electrical discharge (collision with electrons), or when they selectively absorb electromagnetic radiation energy from other photons. This is a natural process that occurs all the time around us, but as its magnitude is very small and very narrow in the visible spectrum, we cannot see it. The location on Earth where we can more easily observe this phenomenon is, for example, near the North Pole, with the famous Northern Lights or auroras. It is produced by the impact between air molecules and cosmic particles from the sun that constantly bombard Earth, producing a phenomenon of luminescence in the upper atmosphere (Fig. 3b).

However, atoms can also decay producing light radiation in a stimulated form. In 1917, Albert Einstein postulated and proved the existence of this mechanism (Siegman 1986; Wright and Fisher 1993; Arndt et al. 1997). When an excited atom collides with a photon, it instantly emits a photon identical to the first (Fig. 3a). This stimulated emission follows the following basic laws:

(a) The stimulated photon travels in the same direction of the incident.
(b) The stimulated photon synchronizes its wave with the incident.

In other words, the waves of the two photons align their peaks adding their magnitudes and thereby increasing the intensity of the light. Photons with aligned peaks produce a coherent (organized) light. In a coherent beam, light travels in the same direction, in the same time, and with the same energy.

The end result of a stimulated emission is then a pair of photons that are coherent and that travel in the same direction. The stimulated emission of light is the working principle of a laser, invented more than 50 years after the discovery of Einstein.

Light Amplification

To illustrate the generation of light inside a laser, let us first imagine a rectangular box or a tube, as a straight cylinder, with a large amount of identical atoms or molecules. As an example, a fluorescent lamp tube with its gas. At each end of the tube, we place mirrors, which because of the construction will be parallel to one another. At one end, the mirror is totally reflective (100% mirror), and at the other end (the exit window of the light – output coupler), the mirror is partially reflective (80% mirror), so that part of the light is reflected back to the tube and part is transmitted through the mirror to the outside (Wright and Fisher 1993; Kulick 1998; Boechat 2009; Raulin and Karsai 2011; Kaminsky Jedwab 2010).

Let us also imagine that the atoms are excited to a higher-energy level by an external source (a light source or an electrical discharge), as if we had activated the switch turning on the lamp. Through the mechanism of spontaneous emission, which takes place completely randomly, the atoms emit photons that begin traveling in various directions within the tube. Those hitting against the tube wall are absorbed and lost as heat, disappearing from the scene. In the case of a lamp, they leave the tube into the environment, illuminating the room. On the other hand, the emitted photons traveling parallel to the tube axis are likely to find other excited atoms and thus stimulate the emission of additional photons, which are consistent with the stimulating photon and travel in the same direction – i.e., along the longitudinal axis of the tube. These two photons continue their journey, again with the likelihood of stimulating, through a similar process, two additional photons – all consistent with each other and traveling in the same axis. The progression continues indefinitely, and 8, 16, 32, 64, etc., photons are produced, all traveling in the same direction, as illustrated in Fig. 4.

It is clearly established a light amplification process that generates a large luminous flux in the longitudinal direction of the tube.

The mirrors perpendicular to the tube axis reflect the photons back intensifying this effect of amplification. Each of these reflected photons traveling along the axis in the opposite direction contributes to the chain reaction effect generating a stream of coherent photons. When they reach the partially reflecting mirror, 80% of the photons return to the tube continuing the amplification

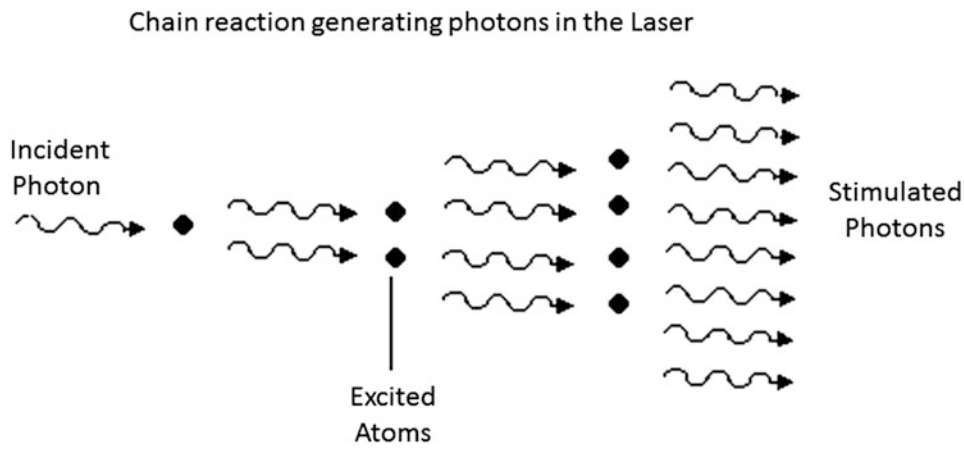

Fig. 4 Chain reaction producing photons inside the laser resonator

effect. The remaining 20% goes out forming the laser beam (Fig. 5a, b). They represent in absolute terms a very intense beam of photons produced by the amplification effect. The tube and its excited medium, together with the mirrors, are called the resonator (or oscillator) which is the basic components of a laser in addition to the excitation source.

Characteristics of a Laser Light

As described above, the laser light has unique properties that make them different from other light sources (Goldman and Fitzpatrick 1994; Arndt et al. 1997; Kaminsky Jedwab 2010; Sardana and Garg 2014):

(a) **Monochrome**: it is generated by a collection of identical atoms or molecules; thus, all photons emitted have the same wavelength, a single frequency. This feature is important because of the selective absorption of the human tissue, which will be presented in the next section.
(b) **Coherent**: because of the stimulated emission and the way the light is amplified, which is only in the longitudinal direction inside the resonator, the photons are organized, as soldiers marching in a military parade. This is called spatial and temporal coherence. At any point of a laser beam, the photons (or light):
   (a) Have the same power
   (b) Travel in the same direction
   (c) Travel at the same time

Being coherent, light from a laser is called collimated. Traveling parallel to the tube axis, the laser beam has a very small divergence angle, i.e., the light does not spread; the photon beam is collimated (parallel). The small divergence allows the use of a lens system to concentrate all the energy of the laser in a precise way on a small focal spot (spot size), achieving a greater concentration of light energy or brightness. Optical laws tell us that the smaller the divergence, the smaller the focal point. When we focus a common light source such as a lamp, of incoherent light, the focal point will be too large and imprecise, whereas when using a laser, we have a very fine and extremely precise focal point and therefore a much more intense effect on the tissue.

Energy, Power, Fluence

The increase of temperature or the effect of treatment on the tissue depends on the amount of energy that it receives. The energy, power, and fluence (energy density) are the physical parameters that control the treatment effect and determine the eventual increase in temperature.

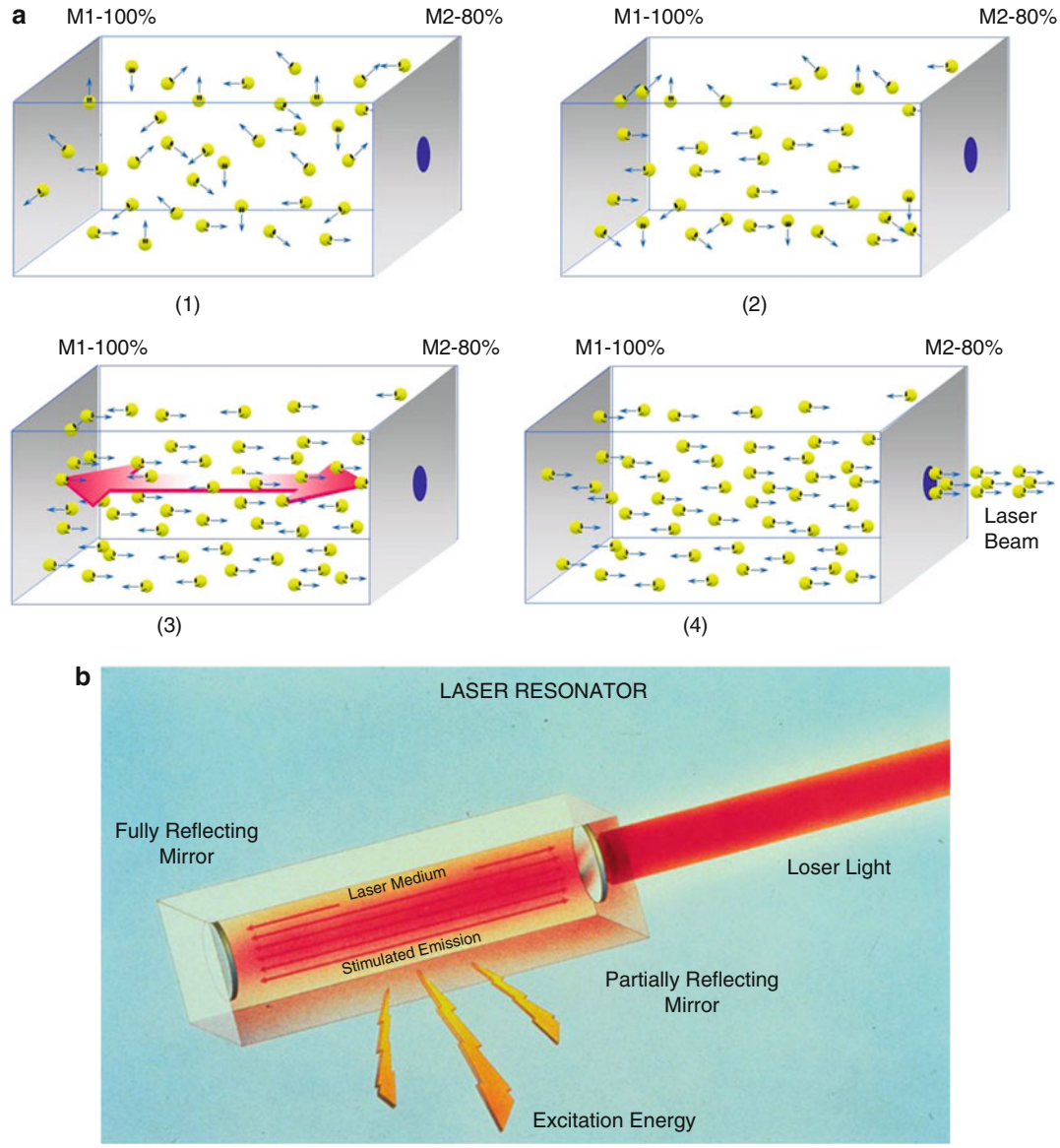

Fig. 5 (**a**) Light amplification and laser beam formation inside a laser resonator. M1 is the 100% reflection mirror and M2 is the 80% partial reflection mirror. The (*1*) and (*2*) are excited atoms that produce photons that begin to travel longitudinally along the resonator between the mirrors. The (*3*) and (*4*) are the photons traveling parallel to the axis of the resonator that stimulate new photons, producing the laser beam. (**b**) Schematic of the laser operation

Energy: is measured in Joules (J).
Power: is measured in Watts (W).

These are different parameters and they are related trough the following equation:

$$\text{Energy(J)} = \text{power(W)} \times \text{time(sec)}$$

Thus, energy is the amount of power delivered to the tissue in a given time, or the laser pulse duration. The thermal effect of the laser is highly localized. In this way, the physical quantity that governs the thermal response of the tissue is the amount of energy delivered to a certain area, the overall size of the application area or the "spot

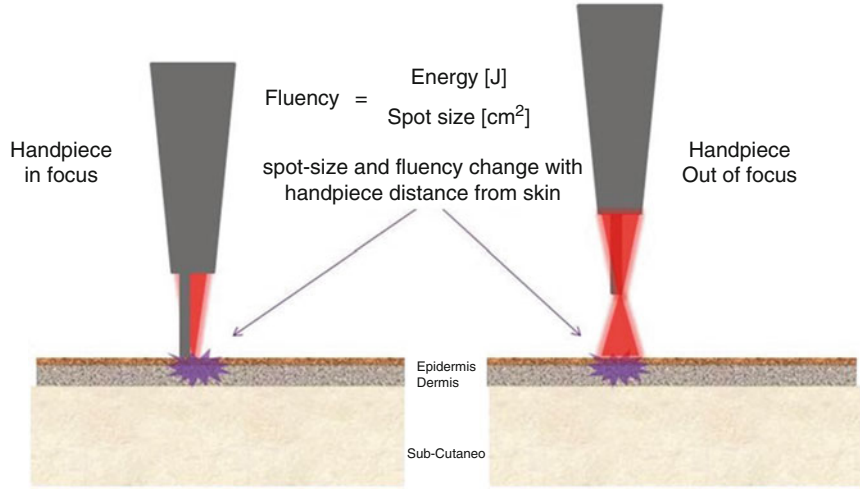

Fig. 6 Focused headpiece. Laser in focus: power density is at its maximum (vaporizing, cutting). Out of focus: power density is reduced (coagulation, milder treatment)

size" produced by the laser handpiece. Thus, the energy density or fluence is measured in J/cm^2:

$$\text{Fluence}\left(\text{J}/\text{cm}^2\right) = \text{Energy}(\text{J})/\text{Area}\left(\text{cm}^2\right)$$

The higher the fluence, the faster the temperature increases in the tissue and consequently the intensity of the desired effect. The effect of the treatment is achieved both by varying the laser output energy and the laser pulse duration, at the tissue application area. All commercial lasers allow us to change easily and continuously the energy.

For a fixed operating power, we can vary the fluence in the tissue by changing the application area (spot size – changing the lens that focuses the laser beam in the handpiece) or by varying the distance of the handpiece from the tissue in a "focused" handpiece.

When we work with light in focus (Fig. 6), the power density is at its maximum because all the energy of the laser is concentrated in a small focal point (usually of the order of 0.1–1 mm), called "spot size." At the focal point, it is possible to precisely cut the tissue and the application has its maximum effect. When we move the handpiece away from the tissue to a defocus, or out of focus position, the application area becomes larger reducing the power density (fluence) and increasing the temperature in the tissue. At this position, the effect becomes milder, producing a superficial effect of vaporization and coagulation (used in skin rejuvenation – skin resurfacing).

Another widely used laser handpiece is called "collimated." Here the laser beam remains parallel (collimated) and constant regardless of the distance from the tissue. It is used in hair removal systems and various types of skin treatment, such as tattoo and melasma removal (Fig. 7).

It is important to note how the cutting effect is controlled when using a laser. The surgeon is used to control the depth of the cut by the pressure exerted on the blade against the tissue. In the laser, as there is no mechanical contact with the tissue, the cut is determined by two factors:

1. Hand movement speed
2. Laser energy

The speed is linked to tissue exposure time, because if we keep the laser acting on a point indefinitely, it begins to vaporize layer upon layer of tissue increasing the depth of the cut. Thus, for a constant power if the surgeon moves the hand slowly, he or she will produce a deep cut. Likewise, for a movement with constant speed, the cutting will be deeper for a greater energy.

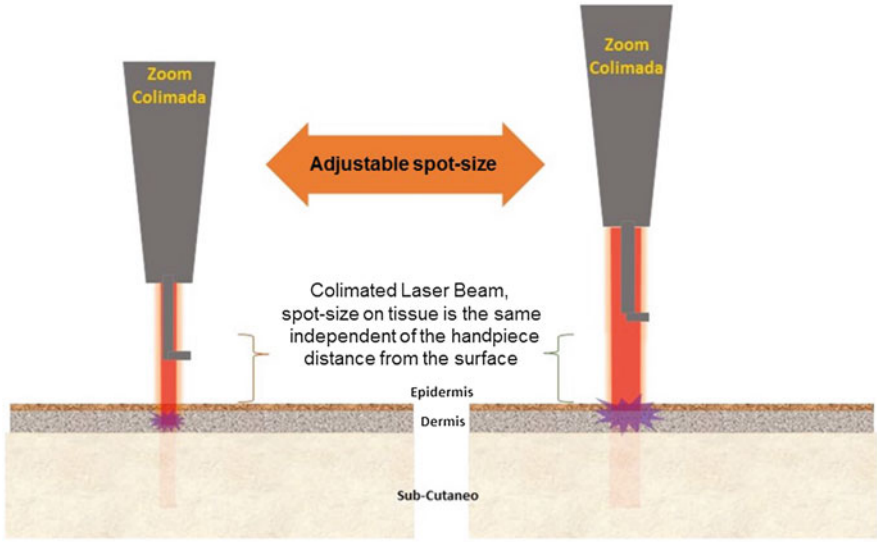

Fig. 7 Collimated handpiece. Regardless of the distance from the skin (touching or moving away), the spot size and fluence remain the same. Some handpieces have a zoom effect that allows the adjustment of the spot size

The laser exposure time also governs the amount of adjacent tissues which may be affected. Modern laser systems have mechanisms that quickly deliver energy to the tissue minimizing the thermal effect in adjacent areas. These mechanisms can be through ultrafast pulses ("ultrapulse" laser) or computerized rapid laser beam scanning systems (fractional scanners), used in skin rejuvenation treatments and more recently in fractional treatment systems. The "scanner" divides and moves the laser beam at high speed to position it over the skin minimizing damage to adjacent tissues. They are controlled by computer and can execute different types of scanning, with great precision and control over the amount of tissue being vaporized (Goldman and Fitzpatrick 1994; Arndt et al. 1997; Kulick 1998; Alster and Apfelberg 1999; Alster 1997).

Operating Modes of a Laser

Depending on the effect of the treatment we want to obtain on the tissue, laser systems can operate in the following modes (Boechat 2009; Raulin and Karsai 2011; Kaminsky Jedwab 2010; Sardana and Garg 2014):

1. **Continuous mode – CW**: In this mode of operation (also known as continuous wave), the laser stays on, just as a normal lamp, and emits a light beam of constant energy, as long as we keep the system powered by the foot switch or the power button on the handpiece (available on some devices). It is widely used in surgeries for coagulation or vaporization of tissue.
2. **Pulsed mode**: This mode works as if we turned a lamp on and off; the laser is pulsed electronically with the times and the intervals between pulses controlled by the equipment computer and selected via the panel. The repetition rate or frequency (given in Hz) of the laser pulse can also be programmed. Most lasers used in dermatology work with ultrafast pulses to vaporize the tissue faster than the thermal diffusion time of the skin in order to minimize damage to adjacent tissues, resulting in safe and effective treatments (Fig. 8).

According to the laser pulse duration, pulsed systems can be classified into:

(a) **Long pulses** – 0.001 s, millisecond (ms) 10^{-3} s
   i. Hair removal, varicose veins

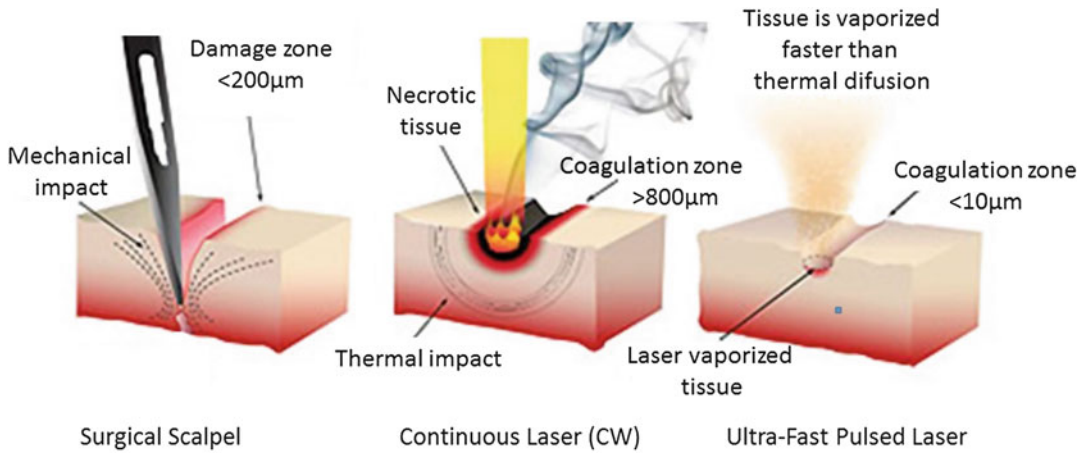

Fig. 8 Comparison of tissue laser cutting, showing continuous wave (*CW*) and ultrafast pulses that minimize the thermal damage to adjacent tissue

(b) **Quasi-CW** – 0.000001 s, microsecond (µs) 10^{-6} s
   i. Skin rejuvenation, onychomycosis, inflammatory acne
(c) **Q-switched** – 0.000000001, nanosecond (ns) 10^{-9} s
   i. Treatment of melasma, tattoo removal
(d) **Mode-locked** – 0.000000000001, picosecond (ps) 10^{-12} s
   i. Tattoo removal and pigmented lesions
(e) **Femto** – 0.000000000000001, femtosecond (fs) 10^{-15} s
   i. Refractive surgery in ophthalmology

Q-Switched: Nanosecond Lasers

This mode is achieved by placing an optical accessory inside the resonator, at the side of the laser crystal, whose goal is to pulse optically the light (Siegman 1986; Goldman 1967; Raulin and Karsai 2011). It is generally used in crystal lasers such as ruby, alexandrite, and Nd:YAG, described below. The goal is to accumulate the laser energy at very high levels and release it at extremely rapid pulses. The result is a very high-peak-power laser pulse (often higher than the common pulse), which can penetrate deep into the tissue, with minimal side effects. Then a shockwave-induced mechanical action caused by the impact of the laser pulse onto the target tissue causes its fragmentation. In the long- and quasi-CW-pulsed modes, the effect is purely thermal.

The classic application is in tattoo removal and the treatment of pigmented skin lesions such as dark circles, postinflammatory hyperpigmentation, and melasma (Goldman 1967; Reid and Muller 1978; Raulin et al. 1998; Chang et al. 1996; Shimbashi et al. 1997; Reid et al. 1990, 1983a; Stafford et al. 1995; Ogata 1997; Chan et al. 1999; Jeong et al. 2008; Mun et al. 2010; Grevelink et al. 1997).

Mode-Locked: Picosecond Lasers

To achieve picosecond pulses, a technique called "mode-locking" is used (Siegman 1986; Raulin and Karsai 2011; Sardana and Garg 2014). The base is a Q-switch system as described above, in which nonlinear effects of the Q-switch crystal are stimulated and modulated inside the resonator in order to create faster pulses with a technique in which only they are amplified. It is more commonly used in crystal lasers as alexandrite and Nd:YAG.

As we will see in the following chapter, the pulse duration governs the way in which light interacts with the tissue (selective photothermolysis), and by varying the pulse duration, we can completely change the laser application in dermatology.

Laser Types

All laser devices consist of the following parts (Siegman 1986; Goldman and Fitzpatrick 1994; Boechat 2009; Kaminsky Jedwab 2010):

1. The resonator/oscillator – with mirrors (total and partial reflectors) and active medium, which, when excited, produces the light and thus determines the wavelength
2. The excitation source (also called pumping) – which delivers power to the active medium producing the photons
3. Laser beam delivery system from the source to the hand of the operator
4. Handpiece, with focusing lens or a scanning system

The industry uses various elements in the manufacture of laser sources in order to cover a growing range of electromagnetic wavelengths. Today, we have ultraviolet lasers, visible light, and infrared. For this end, gases, liquids, crystals, fiber optics, and semiconductors (electronic components) are used.

The pumping of each element also varies; thus, electrical discharges, radio frequency, and light sources such as flash-lamps or even other lasers are used.

To carry the laser light from where it is generated in the resonator to the hand of the user who is making the application, various mechanisms are used depending on the wavelength and energy of the equipment. The most common are:

Articulated arm – a set of multiple mirrors positioned at the corners of articulated pipes to allow the freedom of movement in all directions (Fig. 9).

Optical fiber – thin waveguide with a core made of quartz covered with a thin layer called cladding, which is made of a slightly different material and encapsulated with plastic and metal coatings to give it flexibility. It delivers the laser beam by multiple internal reflections; that is, light enters the fiber, reflects on the core/cladding interface, and keeps moving until it exits the optical fiber. Note that at the output of the fiber, the laser beam has a wide divergence and is no longer collimated. In other words, the beam spreads, losing part of its coherence (Boechat et al. 1991, 1993) (Fig. 10).

Bellow we describe some typical commercial laser systems used in medicine, grouped according to the laser medium (Alster and Apfelberg 1999; Alster 1997; Boechat 2009; Raulin and Karsai 2011; Kaminsky Jedwab 2010; Sardana and Garg 2014).

Gas Lasers

Excimer

Gas molecules that exist only in the excited state, called "dimers," form the excited medium; examples are molecules such as halogens combined with noble gases (ArF, KrF, XeCl, Xef). The word "excimer" is an abbreviation of the term "excited dimer." The emission covers some wavelengths in the ultraviolet range such as 193 nm ArF, 222 nm KrCl, 248 nm KrF, and 308 nm XeCl. The pumping is usually made by electric discharge or the shock of electrons with gas molecules. Quartz optical fibers are used as beam delivery system. Since the wavelength is very small and carries a high energy, these lasers are widely used for high precision incisions or tissue ablation, such as in ophthalmic refractive surgery (myopia). In dermatology, this system has shown excellent results in the treatment of psoriasis and vitiligo (Zelickson et al. 1996; Guttman 2000).

Carbon Dioxide (CO_2)

The CO_2 is still one of the most used lasers in surgery, dermatology, and industrial applications. Its power may vary from a few KW up to MW in a continuous or pulsed manner. The laser medium is a mixture of gases including N_2 (nitrogen – 13–45%), He (helium – 60–85%), and CO_2 (1–9%). Pumping is achieved by high-voltage electric discharge or radio frequency (RF). The molecule of CO_2 is excited by mechanical shock with electrons, of the N_2 and He molecules. The wavelength is in the infrared range at 10,640 nm.

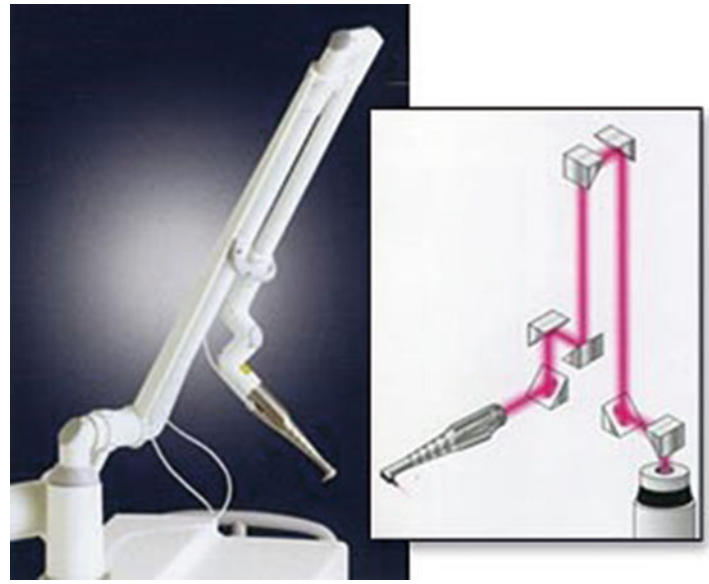

Fig. 9 Diagram of an articulated arm

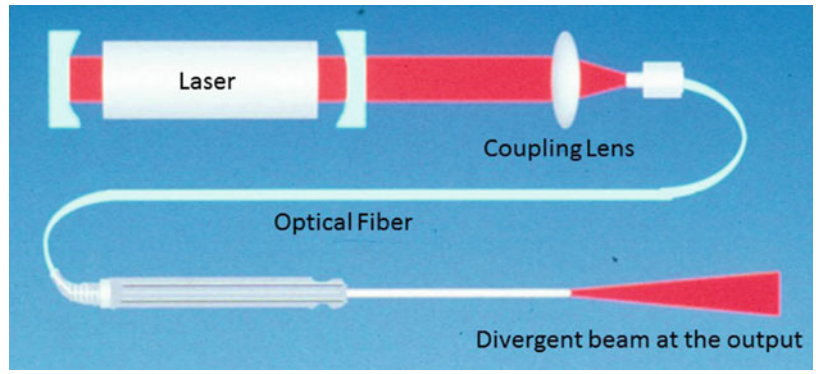

Fig. 10 Diagram of an optical fiber showing the beam divergence at the output

This is a relatively efficient laser (30% of electro-optical conversion), and because of that, it has low power consumption and maintenance. It uses an articulated arm and special dielectric-coated flexible hollow waveguides (Siegman 1986; Kulick 1998; Alster and Apfelberg 1999; Alster 1997; Lask 1995; Pitanguy et al. 1996) (Fig. 11).

Liquid Laser

Dye Laser

It uses a liquid Rhodamine solution (R6G), which is a fluorescent dye, as the laser medium. It is pumped by a flash-lamp or another laser. The wavelength may vary continuously from 300 to 1,000 nm, and the resonator can be tuned. It is most commonly used in yellow (585–600 nm). Its main application is the treatment of vascular lesions and inflammatory processes of the skin. It uses quartz optical fiber (Siegman 1986; Reichert 1998; Mcmillan et al. 1998; Reyes and Geronemus 1990) (Fig. 12).

Solid-State Laser (Crystal)

Figure 13 shows the schematics of the most common solid-state laser systems in the market. The mirrors, the laser rod (the crystal), and the flash-lamp, used for the pumping inside a cavity made of a coated elliptical reflecting material – usually

Fig. 11 RF-pumped CO_2 laser with articulated arm, eCO_2™ (Lutronic Inc.)

Fig. 12 Flash-lamp-pumped dye laser, Vbeam Perfecta™ (Syneron Candela)

ceramic or a large resistance metal such as gold – compose the resonator (Siegman 1986; Boechat 2009).

Ruby: Cr^{3+}:Al_2O_3

It was the first laser developed by Maiman in 1961 (Siegman 1986; Goldman and Fitzpatrick 1994; Arndt et al. 1997; Siegman 1986), but it was some time before this system started to be used in medicine. The medium is ionized ruby crystal. It is pumped by a flash-lamp. The wavelength is in the red range of 694 nm. The nature of the crystal requires high energy for pumping or high-power flash-lamps. It uses fiber optics and articulated arm for laser delivery. It is generally used for the treatment of pigmented lesions, hair, and tattoo removal (Goldman 1967; Reid and Muller 1978; Raulin et al. 1998; Chang et al. 1996; Shimbashi et al. 1997; Yang et al. 1996; Ono and Tateshita 1998; Reid et al. 1990, 1983a) (Fig. 14).

Alexandrite: Cr:$BeAl_2O_4$

The gain medium is chromium-doped chrysoberyl, the semiprecious stone alexandrite ionized. It is pumped by a flash-lamp. The wavelength is at the end of the red range (755 nm). It uses flexible optical fibers or an articulated arm. This crystal has better optical properties, which enables a faster and more efficient operation in a smaller device than the ruby. It is widely used for hair removal and treatment of pigmented lesions (Siegman 1986; Finkel et al. 1997; Stafford et al. 1995; Chan et al. 1999; Alster 1997) (Fig. 15).

YAG Family

The YAG abbreviation is short for yttrium aluminum garnet, which is a synthetic crystalline structure serving as host to the ion that will produce the radiation with the desired wavelength. It is pumped by laser diodes or a flash-lamp, and it works in the near-infrared spectrum. It uses optical fiber and in some cases the articulated arm (high-energy pulsed laser – Q-switched) as the beam delivery system. The most common are (Siegman 1986; Goldman and Fitzpatrick 1994; Kulick 1998; Wong and Goh 1998; Ogata 1997; Chan et al. 1999; Boechat 2009; Raulin and Karsai 2011; Kaminsky Jedwab 2010):

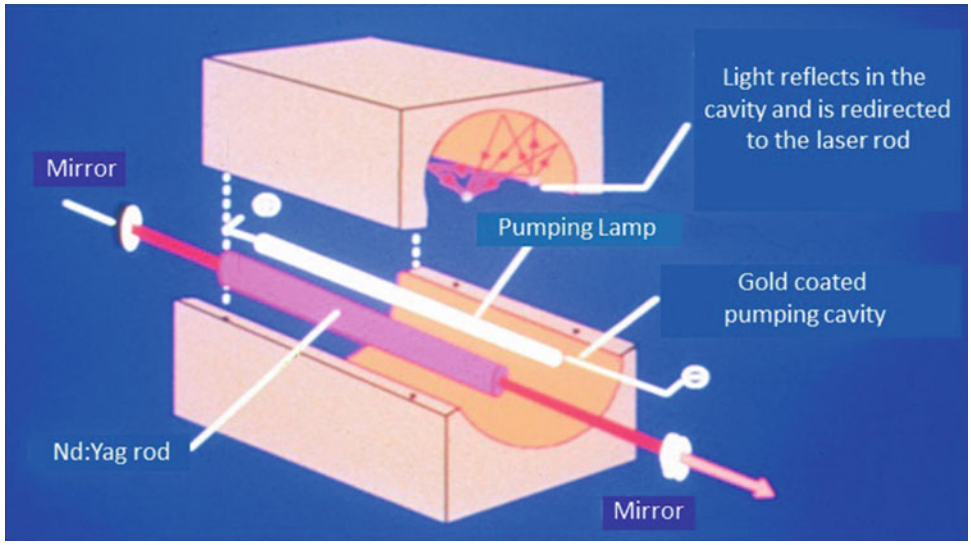

Fig. 13 Schematics of a typical laser using a crystal rod

Fig. 14 Ruby laser with an articulated arm (Asclepion Laser Technologies)

Fig. 15 Alexandrite laser, GentleLase™ (Syneron Candela)

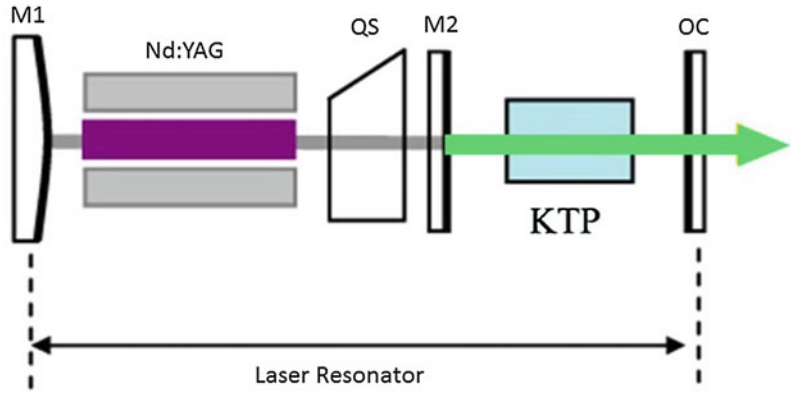

Fig. 16 Schematics of a KTP laser pumped by a Q-switched Nd:YAG laser. M1 is the 100% reflector mirror; M2 is the partial reflector output coupler for the Nd:YAG pumping laser; *QS* Q-switch, *KTP* the KTP crystal, *OC* output coupler and wavelength selector for 1,064 nm and 532 nm

- ***Nd*:*YAG*** – it uses the neodymium ion, with wavelengths of 1,064 nm and 1,320 nm, which is used for non-ablative skin rejuvenation (Muccini et al. 1998; Goldberg 1999, 2000).
- ***Nd*:*YAG*/*KTP*** – by placing a second crystal in the laser resonator, in general the "famous" potassium-titanium-phosphate (KTP), it generates the frequency-doubled Nd:YAG laser with a green wavelength at 532 nm. It is used for removal of superficial pigmented and vascular lesions (Figs. 16 and 17).
- ***Nd*:*YAG*/*KTP* + *handpiece with crystal dye*** – a solid-state fluorescent dye handpiece can still be added to these lasers in order to obtain different wavelengths, such as 595 nm (yellow) and 650 nm (red), thus making the machine extremely versatile for the treatment of pigmented lesions and the removal of light-colored tattoos at different depths (Fig. 18).
- ***Ho*:*YAG*** – it uses holmium ions, with wavelength of 2,100 nm. It is excellent for treatments in bone and cartilage and for the fragmentation of kidney stones.
- ***Er*:*YAG*** – it uses erbium ions, with wavelength of 2,940 nm. It is well-known for its use in "skin resurfacing" (skin rejuvenation) (Fleming 1999; Weinstein 1998) (Fig. 19).
- ***Tm*:*YAG*** – it uses thulium ions, with wavelength of 1,927 nm. It is used for non-ablative skin rejuvenation with a more superficial action.

Fig. 17 Laser system Spectra XT™ with two wavelengths: Nd:YAG (1,064 nm) and KTP (532 nm), Lutronic Inc.

Nd:YAP

It uses neodymium ions in yttrium aluminum perovskite crystal, with wavelength of 1,340 nm. It is used for non-ablative skin rejuvenation and chronic inflammatory diseases such as hidradenitis (Milanic and Majaron 2013; Antonio et al. 2015).

Fig. 18 Crystal dye handpieces, laser Spectra XT™ (Lutronic Inc.)

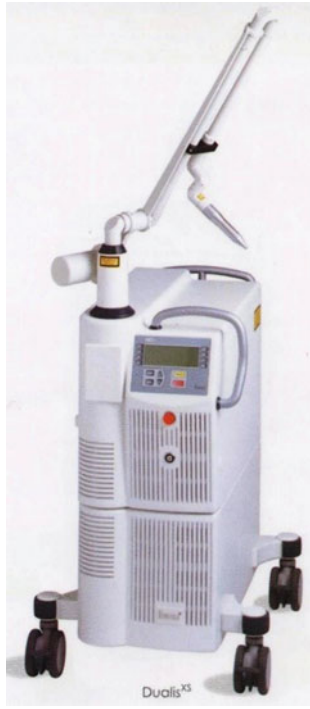

Fig. 19 Er:YAG laser system, with articulated arm for ablative skin rejuvenation (Fotona)

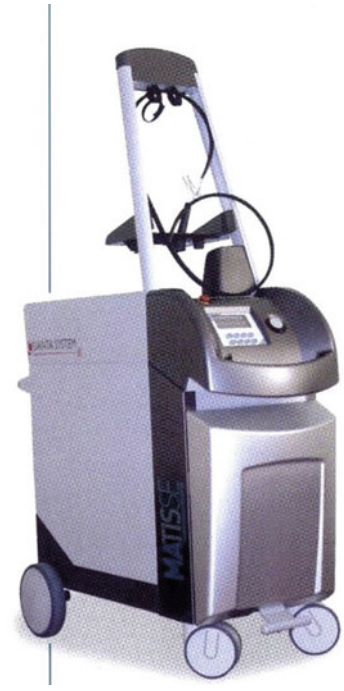

Fig. 20 Fractional Er:glass laser system, Matisse™ (Quanta System)

Er:Glass

The gain medium is changed for crystal glass, which serves as host for the erbium ion. The wavelength shifts to 1,540 nm, in the near infrared. It is used for deeper skin rejuvenation and employed in fractional laser systems (Mordon et al. 2000) (Fig. 20).

Er:YSGG

The gain medium is similar to the YAG crystal, and it uses the erbium ion in an yttrium scandium gallium garnet (YSGG) host. The wavelength is also in the near infrared, 2,790 nm, used in the Pearl™ handpiece of Cutera. The main application is fractional skin rejuvenation. It is an alternative to the Er:YAG laser skin resurfacing.

Semiconductor Laser

– **Diode** – the laser medium is a semiconductor, i.e., an electronic component. It is pumped by electric current. The changing of the semiconductor achieves a wide range of wavelengths ranging from the visible, 450 nm, to the near infrared, 1,400 nm. The most common are AlGaAs (aluminum gallium arsenide) with wavelengths from red to near infrared, 620–900 nm, and GaAs (gallium arsenide) in the near infrared, 830–920 nm. It has a very efficient electro-optical conversion (greater than 50%); thus, generally it is a small and greatly simplified operation system. It uses optical fibers or simply free, handheld devices. Some equipment manufacturers provide systems with one or more laser diodes with different wavelengths, increasing the flexibility of the system. It is widely used for hair removal, non-ablative skin rejuvenation, and treatment of vascular lesions. It is also used for pumping other lasers such as Nd:YAG, Nd:YAG/KTP, and fiber-optic lasers, as we will see below (Siegman 1986; Goldberg 2000; Ross and Hardway 2000; Lou et al. 2000) (Fig. 21).

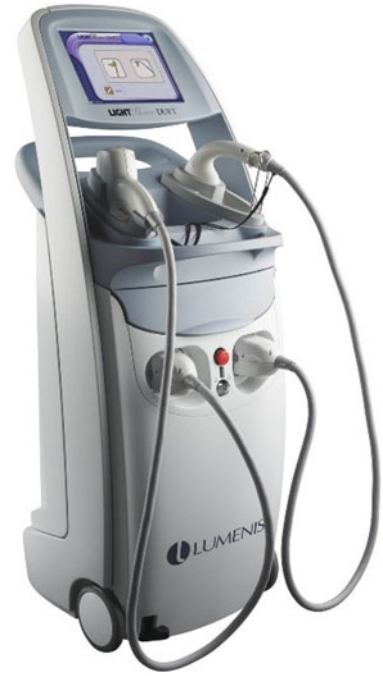

Fig. 21 LightSheer Duet diode laser, 810 nm (Lumenis)

Optical Fiber Laser

Extremely robust, long-lasting, and highly reliable, this technology employed in undersea optical telecommunications cables has found an application in medicine in the development of fractional lasers (Manstein et al. 2004; Geronemus 2006; Raulin and Karsai 2011).

– **Y, Er:fiber** – the gain medium is a quartz optical fiber measuring only 150 μm in diameter, containing erbium and yttrium ions. It is pumped by laser diodes. The wavelength is 1,550 nm. The system does not need optical components such as mirrors, output couplers, flash-lamps, and cooling system, which significantly reduces the need and cost of maintenance. This new technology produces microscopic focal points on the skin of the order of 100 μm (approximately the thickness of a human hair), since the light source is also a microscopic fiber, leading to the advent of fractional skin treatment (Fig. 22).

LED: Light-Emitting Diode

LEDs are electronic components, or semiconductor diodes, that emit light when stimulated by electric current. They may be considered as relating to laser diodes, since they are manufactured with the same materials, as GaAs, GaAlAs, and GaInPAs, and thus provide the same wavelengths. However, they do not have the light amplification effect produced by a laser resonator system. In this way, an incoherent monochromatic light is produced that diverges in various directions just as a lamp of low intensity (Boechat 2009; Raulin and Karsai 2011; Kaminsky Jedwab 2010).

In order to concentrate and direct the emitted light, they are manufactured with a parabolic plastic housing, which functions as a small lens (Fig. 23).

Fig. 22 Optical fiber laser, Mosaic™ (Lutronic Inc.)

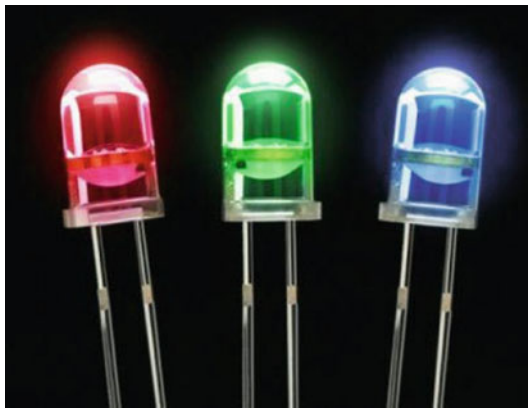

Fig. 23 Example of LEDs

LED treatment systems use panels made of 1,000–2,000 components in order to extend and optimize the application area. Depending on the application or treatment, it is possible to change the panel to a different wavelength. Some manufacturers have integrated LEDs with different wavelengths on the same panel thus avoiding the need to change them (Fig. 24a, b).

Some of the most common applications are in the biomodulation of cells, described below and in the following chapters, such as anti-inflammatory effects and improved wound healing. It is also used in photodynamic therapy and teeth whitening.

Intense Pulsed Light

It is a system that employs a flash-lamp for many applications, but it is not a laser light source, pulsed light, or intense pulsed light – IPL. Dr. Shimon Eckhouse at ESC Medical in Israel developed this concept, in the nineties (Boechat 2009; Raulin and Karsai 2011; Kaminsky Jedwab 2010).

It uses an electronically controlled intense flash-lamp. For this reason, it has distinct characteristics from a laser source:

(a) **Polychromatic**: it emits a broad spectrum of wavelengths, generally in the range from 400 to 1,200 nm. It uses band-pass filters placed in front of the lamp for wavelength selection. These filters remove a band of wavelengths, in general those below the filter specification, letting through all the wavelengths above it. Some machines use a more complex filter, which narrows the emission at a range of wavelengths, as illustrated in

Fig. 24 (**a**) LED panel, Hygialux™ (KLD). (**b**) LED panels with different wavelengths (KLD)

Fig. 25 a–c. Even with a narrow emission spectrum limited by the filters, the emitted energy disperse within several wavelengths, that is those that will be absorbed by the tissue to be treated and others that will have no effect. Thus, the selectivity and effectiveness of the treatment are reduced as compared with a laser that has 100% of the energy concentrated in a single wavelength (monochromatic).

(b) **Incoherent**: Different from a laser source, the IPL energy is emitted in all directions; it spreads. Mirrored surfaces placed behind the lamp, similar to reflectors used in car headlights, concentrate and direct the light. It will have a more superficial and mild effect on the tissue because it is less intense than laser light. The application will also be less painful.

The multiplicity of emitted wavelengths makes these systems very versatile, being able to perform several applications such as in hair removal, pigmented lesions, non-ablative rejuvenation, and vascular lesions, by simply changing the filter and pulse duration (Fig. 26).

These systems generally have a fixed pulse duration already set by the manufacturer depending on the application. To change the pulse duration, in general, it is necessary to change the entire handpiece. Pulse duration is restricted to the range of milliseconds because of the lamp characteristics; however, it suits most skin applications.

Treatment Platforms

Following the trend of the market to produce increasingly compact systems, which provide various applications, the laser industry has developed the concept of multi-application platform. These systems consist of a base (platform) that carries the energy source and cooling system. Then several handpieces can be connected to the base providing different applications. Each handpiece may contain an IPL or a laser system. The most frequent applications are hair removal, skin rejuvenation, treatment of pigmented and vascular lesions, and tattoo removal (Raulin and Karsai 2011; Kaminsky Jedwab 2010; Sardana and Garg 2014).

These treatment platforms became very popular because of the excellent cost/benefit and versatile combination of intense pulsed light and laser in the same equipment. There are also platforms that have only lasers, or only IPL, and others that added a RF handpiece for skin tightening (Fig. 27).

After becoming familiar with these technologies and their operating principles, a question comes to mind: when and how to use each of these systems?

The application of each laser, IPL, or LED in dermatology will depend on the response of the tissue to the wavelength being used.

Light-Tissue Interaction

Light can interact with living tissue in the following forms (Anderson and Parrish 1981; Goldman and Fitzpatrick 1994; Arndt et al. 1997; Kulick 1998):

Photothermal: light energy is absorbed by the target tissue (chromophore) and transformed into heat, causing coagulation or vaporization.

Photomechanical: fragmentation by mechanical effect, as in the Q-switch described above.

Photochemical:

1. Direct breaking of chemical bonds between atoms of a molecule produced by, for example, an ultraviolet excimer laser when sculpting a cornea, thus with great accuracy.
2. Light activates a chemical reaction that produces reactive free radicals, as in photodynamic therapy (PDT), described in a following chapter.

Photobiomodulation: light is used to modulate intra- and intercellular activities. It employs low-power laser and LED panels. It has anti-inflammatory action and the effects of wound healing and tissue regeneration (Lopes 1999).

Selective photothermolysis: it is the art of combining wavelength, pulse duration, and energy to obtain the desired effect on the target tissue preserving adjacent areas, as described below.

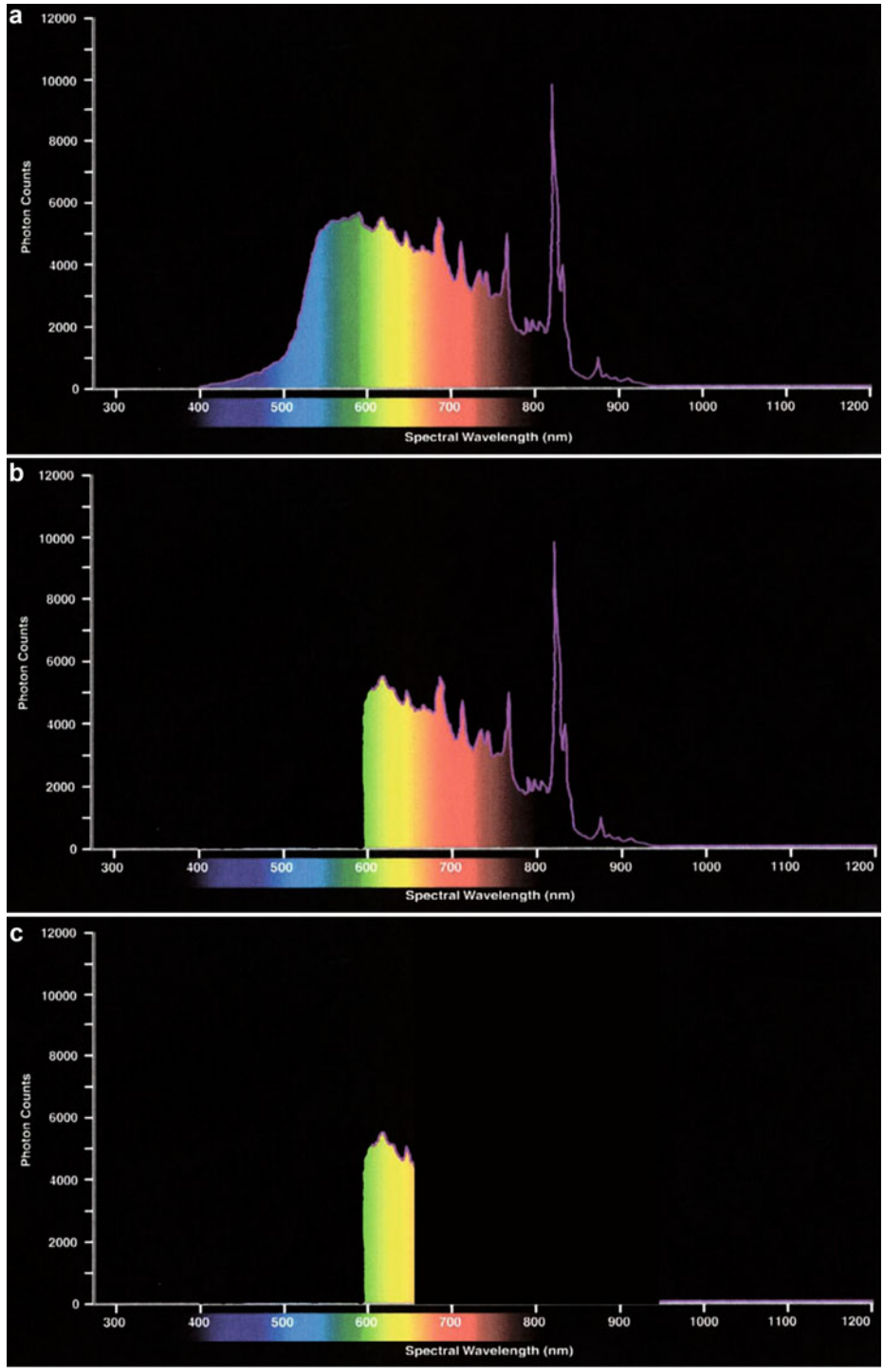

Fig. 25 (**a**) General output spectrum of an IPL, (**b**) with a single 570 nm cut filter and (**c**) with a band-pass filter that limits even further the output spectrum

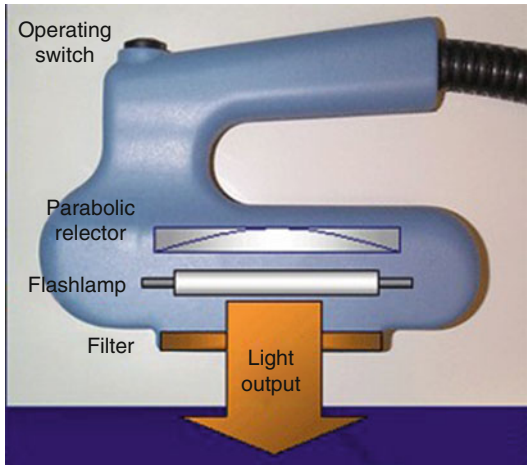

Fig. 26 Schematics of an intense pulsed light – IPL (Lumenis)

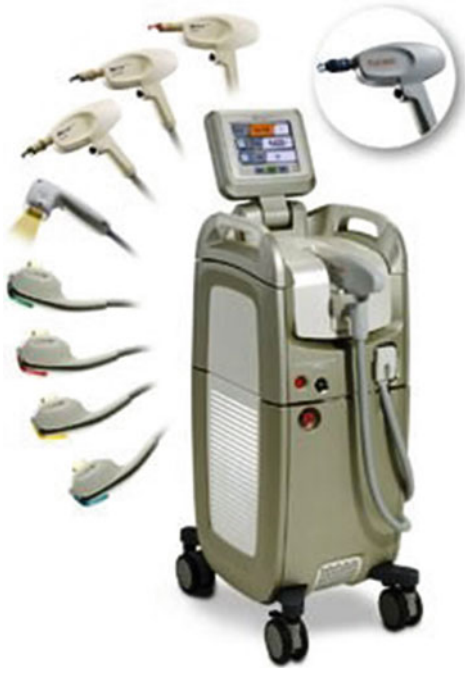

Fig. 27 Treatment platform Harmony™ with several handpieces (Alma Lasers)

When a beam of light hits the tissue, it is (Fig. 28) partially transmitted, reflected, spread (scattering), or absorbed.

Laser light will only produce a therapeutic effect if the target tissue is "in tune" with the energy that is being used, as in a mobile phone. At any given time, there are thousands of mobile phone waves passing where we are, but the phone does not ring. It will only be triggered when the emitted wave is in tune with the device. Similarly, we can place several wavelengths of light in the skin, but the target tissue will absorb only a specific light. In particular, the energy deposited by the most commonly used lasers in medicine is transformed into heat and thus produces a temperature increase on the chromophore.

The laser parameter that most influences the absorption factor, also called the "tuning" effect, is the wavelength of the light (its color; its frequency). Each part of our organism or component of our skin responds differently or has affinity to a particular wavelength. Certain tissues are transparent to a particular laser; others absorb it completely. Therefore, we can induce the necessary thermal effect to treat it selectively at a specific point without affecting the surrounding tissue, giving rise to the phenomenon of the "selective photothermolysis" theory developed by Dr. Rox Anderson et al. in Boston, USA (Anderson and Parrish 1981, 1983; Goldman and Fitzpatrick 1994).

The graph of Fig. 29 represents the fundamental result of the publication of Anderson et al. (Anderson and Parrish 1981; 1983). It shows the variation with wavelength of the absorption coefficient of certain skin components, such as melanin, hemoglobin, and water molecule. We can see that melanin has a high absorption for lasers in the visible range, such as green (KTP), which can be used, for example, in the treatment of pigmented lesions. Hemoglobin has an absorption peak in the range of yellow light (dye laser), making it a good option for treating vascular lesions. The ruby laser, in the range of red light, is well absorbed by the melanin and dark pigment in the skin. On the other hand, it is positioned at a minimum for hemoglobin absorption, which explains in part the difficulty that these systems have to remove red pigments in the treatment of tattoos and vascular lesions (low coagulation effect).

When the light of these lasers enters the skin in fast pulses, or rather ideal pulses, it is able to cross

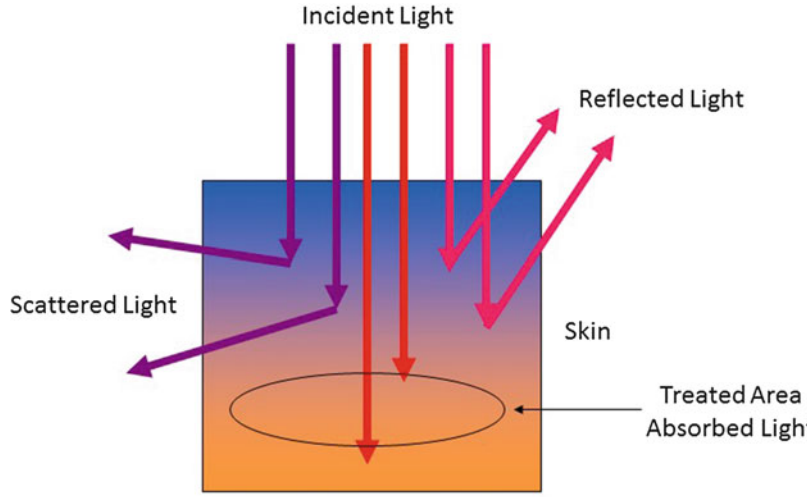

Fig. 28 Light-tissue interaction

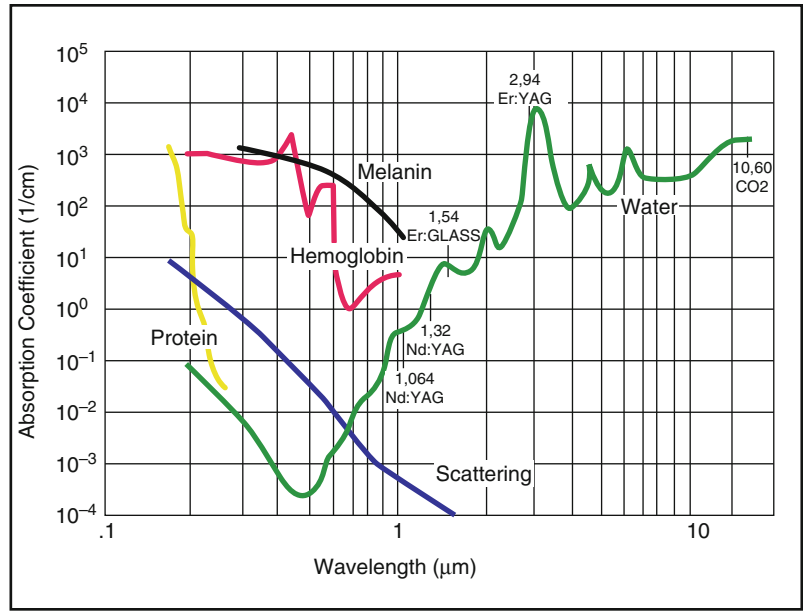

Fig. 29 Curve of the absorption coefficient of some tissue components as a function of wavelength, pointing out the most popular laser systems

the skin without causing any damage and is absorbed only by the target tissue with which it has affinity. These components are referred to in the literature as "chromophores."

We also note from the graph that the absorption of melanin in the visible and near infrared (invisible) is very wide which allows for a number of different lasers to be used effectively for treating pigmented lesions and hair removal, such as the 810 nm diode laser and 1,064 nm Nd:YAG. Because of the its longer wavelength, the Nd:YAG penetrates deeper in the skin, as described below, and its absorption coefficient for melanin is lower when compared to visible lasers, such as green. These are properties that make these lasers suitable for a variety of treatments, since they present reduced risk of damage of the skin surface, because of the absorption of melanin, and are effective for dermis treatments such as deep vascular lesions and melasma.

The Er:YAG (2,940 nm) and CO_2 (10,600 nm), in the infrared, have high absorption coefficients

for water molecule. As water is the major component of the cellular structures, its interaction with these wavelengths is predominant. Therefore, the first layers of cells rapidly absorb the energy from these lasers increasing their temperature to the vaporization level, making it an excellent tool for cutting or precise and superficial tissue removal, such as in laser skin resurfacing or fractional laser skin resurfacing. The Er:YAG laser wavelength is at the peak of water absorption, with a coefficient at least ten times higher than the CO_2 laser. Since its light is more rapidly absorbed, the energy penetrates less, what makes it have a more superficial action compared to CO_2. The treatment will also have lees thermal effect being gentler to the skin (Chernoff et al. 1995; Alster et al. 1999; Weinstein 1998).

Another important aspect of light-tissue interaction is the laser pulse duration (pulse length or exposure time). This must be such that the energy produces an increase in temperature that is confined (concentrated) to the target tissue, with minimal dispersion to the surrounding areas. In other words, the laser pulse duration has to be long enough to increase the temperature on the target tissue up to its destruction level while being short enough not to irradiate heat to the surrounding tissue. A similar situation happens when we want to verify if the iron is hot enough for ironing clothes. Usually, we place the finger on the iron for enough time to check that it is hot, but remove it very fast to guarantee that we do not burn it.

In order to achieve the correct pulse duration, we need to observe the thermal relaxation time (TRT) of the target tissue.

From what is discussed above, the basic principles of selective photothermolysis are (Anderson and Parrish 1983; Goldman and Fitzpatrick 1994; Waldorf et al. 1997; Klavuhn 2000):

(a) **Ideal wavelength** that is absorbed only by the target tissue or chromophore
(b) **Ideal pulse duration** that should be sufficient to produce the desired effect on any target tissue, but fast enough to cause minimal effect on the surrounding tissues, i.e., confining the energy in the chromophore
(c) **Energy** enough to reach the treatment effect

In summary, the vast majority of treatments in photomedicine happen as follows:

1. Light is absorbed by the target tissue or chromophore.
2. The absorption of light causes a selective heating of the target while preserving the surrounding tissues.
3. The chromophore selective heating causes its coagulation or vaporization, reaching the goal of the treatment.

Light Penetration Depth

Giving great importance to the effectiveness of the treatment, light penetration depth is primarily governed by the wavelength, observing the following factors (Anderson and Parrish 1981; Raulin and Karsai 2011; Sardana and Garg 2014; Lapidoth and Halachmi 2015):

1. Scattering of light in the visible part of the spectrum.
2. Absorption by water in skin cells, particularly the epidermal ones on the near-infrared wavelength range.
3. For a given wavelength, the higher is the energy, the deeper the energy will reach.

Going back to the graph of absorption coefficient of Fig. 29, we see that light scattering (blue curve) becomes stronger for smaller wavelengths on the visible range. Therefore, for this part of the spectrum, regardless of the energy used, penetration is usually very small as shown in the graph of Fig. 30. The scattering effect begins to reduce in red light (700 nm) and practically disappears in the near-infrared range, around 900–1,100 nm, which allows these wavelengths to penetrate deeply into the tissue. After 1,200 nm, the absorption of the water in the chromophore present in abundance in the skin cells starts to become significant, again reducing the light penetration.

As it penetrates the skin, light energy is absorbed and scattered along the way, decreasing

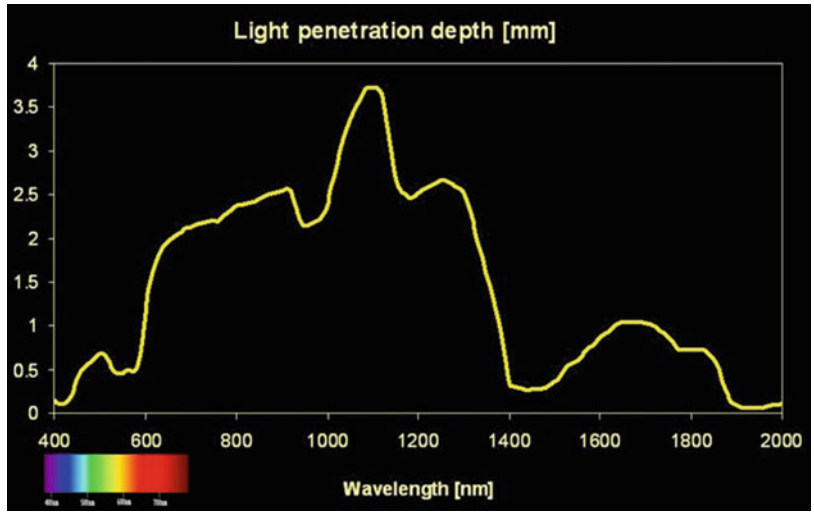

Fig. 30 Light penetration depth as a function of the wavelength

the intensity until it disappears. The power distribution along the light path in the tissue will reduce as it penetrates the skin. The energy in the surface is always higher than at any point within the tissue. Therefore, for a given wavelength, light with higher energy at the surface will have a slight increase in tissue penetration.

In summary, visible wavelengths are ideal for the treatment of superficial lesions such as spots or port-wine stains. It is common to observe in the treatment of superficial pigmented lesions that some spots do not clear completely. This can indicate that part of the spot is located on a deeper layer where light does not reach.

Wavelengths on the range of 900–1,100 nm should be used for the treatment of deep lesions such as varicose veins or hemangiomas and dermal melasma.

Another mechanism can control the light penetration depth. For a given wavelength and fluence (energy/application area), it is possible to achieve a greater energy penetration by increasing the spot size. Figure 31 illustrates the effect of the spot size on light penetration. Using a small spot size, it is not possible to achieve the concentration of light deep into the skin because of the scattering. For a larger spot size, the dispersion is the same, but it compensates the scattering effect by achieving a greater energy concentration deeper into the skin. Therefore, the larger the spot size, the greater the energy concentration or the deeper the penetration. This effect is important, for example, in laser hair removal, treatment of dermal melasma, and tattoo removal (Raulin and Karsai 2011; Kaminsky Jedwab 2010; Sardana and Garg 2014).

Fractional Laser Systems

To appreciate the revolution introduced by the fractional laser technology, let us imagine a patient who seeks an aesthetic improvement of the skin as a family photograph that needs some finishing touches. Today, a photograph is digitally altered pixel by pixel, to improve the appearance of objects in the image. Likewise, damaged paintings are restored gently in a small area at a time.

This same concept is employed in systems that use the fractional photothermolysis technology. The laser produces microscopic thermal injury called microthermal zones (MTZ), approximately 100–150 μm in diameter – the thickness of a human hair – and depth from 0.2 to 2.4 mm (IPL devices in general achieve a maximum of 0.3 mm below the surface). These MTZs are surrounded by healthy tissue that is not affected and will help in the recovery of the micro-damaged area. The surrounding tissue will also be mobilized in the overall skin regeneration process. The resulting rejuvenation effect is comparable to deep

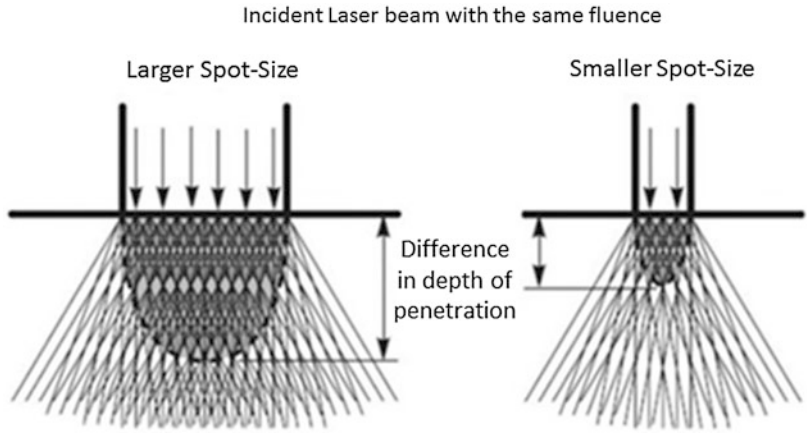

Fig. 31 Spot size effect on the penetration depth of a laser beam with the same fluence

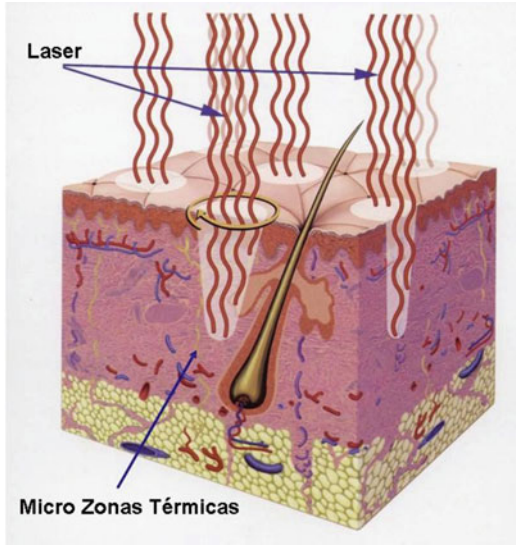

Fig. 32 The science of fractional photothermolysis

chemical peels or dermal mechanical abrasion, but with minimal side effects and little downtime (Fig. 32).

An intelligent scanning system (optical scanners) located on the handpiece ensures the even distribution of MTZs. The operator can choose directly in the laser panel the amount of MTZs that will be put on the skin or the percentage of the total skin area that will be stimulated, controlling the aggressiveness of the treatment. More MTZs means greater stimulus, being more aggressive the application and consequently showing more results. This leads to an application control that hitherto did not exist in dermatological treatments.

The method was developed by the parents of selective photothermolysis, Doctors Rox Anderson and Dieter Manstein, at the Wellman Laboratories in Boston, USA. The first fractional laser system, the Fraxel SR, was shown by Reliant Technologies Inc. in the Congress of the American Academy of Laser (American Society for Laser in Medicine and Surgery – ASLMS) in April 2004 (Laubach et al. 2005; Geronemus 2006; Raulin and Karsai 2011; Munavalli et al. 2005; Khan et al. 2005).

The system follows the principles of selective photothermolysis with wavelength in the 1,550 nm range, where the water of the chromophore is present in the skin cells. In its original design, the fractional systems perform a non-ablative treatment, preserving the skin surface, and the temperature of the tissue increases only up to the coagulation point, producing microthermal zones. Treatment takes three to five monthly sessions.

Beyond the minimum recovery time, the advantages of this treatment include the possibility to use the laser to treat other regions of the body besides the face with safety and efficacy and to remove deep pigmented lesions, and also there are surprising results on the improvement of unaesthetic and acne scars. The following chapters will discuss in detail applications of fractional treatment.

Some commercial non-ablative fractional systems are:

Fraxel re:Store – 1,550 nm wavelength, Er:fiber laser. It has a handpiece with an intelligent continuous scanning system that measures the speed of the application of the operator to distribute the MTZs on the skin homogeneously.

Palomar Lux1540 – it has a fractional handpiece of the Palomar StarLux platform, which employs an Er:glass laser. It uses a fixed filter at the output to split the beam and to generate the fractional effect. Thus, the number of MTZs and application area is fixed.

Lutronic Mosaic – it is a fractional system from Lutronic Inc., which is a Korean company that also employs an Er:fiber laser with wavelength at 1,550 nm. It uses the intelligent scanner at the handpiece; thus, it is possible to choose the number of MTZs (density of the treatment), and the application can be in a static or continuous scan mode, as Fraxel (Fig. 22).

The great success of the fractional technology led to the diversification and improvement of the method originating the ablative fractional treatment. The laser drills micro-holes with controlled depth in the skin, with a thin tissue coagulation zone around them. The surface is damaged producing small crusts and more persistent erythema. The recovery time is longer, and there are restrictions on the skin type and body areas to be treated.

The ablative fractional treatment brought back the CO_2 laser to the rejuvenation scenery because it gave control, safety, and less restriction to the previous efficient CO_2 laser skin resurfacing that still remains the gold standard of skin rejuvenation. Another advantage is that it can also be used for precise cuts and vaporization in minor surgeries.

Bellow, we show some examples of commercial fractional ablative lasers:

Lutronic eCO$_2$ – it is a CO_2 fractional laser with static and dynamic scanning system (Fig. 7). It is possible to program the diameter and density of MTZs.

Fraxel re:pair – it is a CO_2 laser, which uses the same fractional technology as the non-ablative Fraxel re:Store with an intelligent continuous scanning system.

Lumenis Total Active FX – it also uses a CO_2 laser with intelligent scanners, which allow for static and dynamic scanning modes. The diameter and density of MTZs can be programed.

Deka SmartXide^2 DOT/RF – it is a CO_2 laser with scanners and radio-frequency (RF) technology integrated in the handpiece.

Alma Pixel CO$_2$ – it is a CO_2 laser with an array of micro-lenses on the tip to split the beam and to produce the fractional effect. The number and diameter of MTZs are fixed although it offers handpieces with different sizes.

Alma Pixel Handpiece – it is a fractional handpiece from the multiplatform Harmony employing an Er:YAG wavelength of 2,940 nm and a filter effect to split the laser beam and to produce the fractional effect. The MTZs are thicker than in the other devices, of the order of millimeters in diameter, and more superficial, reach only the epidermal layer, because of the wavelength and energy of the system.

Radio Frequency

Radio frequency (RF) consists of a high-frequency electric current, of the order of 1 MHz, and has been used in medicine for several years. Just for comparison, household appliances, such as TVs and refrigerators, work with 50 or 60 Hz, which are low frequencies.

Going back to Fig. 1, the chart of the electromagnetic spectrum, we see that RF occupies the kHz to GHz range, used for radio communication, which gave it its name. Medical equipment uses a portion of the narrow band of this range – from 200 kHz to 40 MHz – in different applications. In this frequency range, the effects of stimulation of nerves and muscles decrease, and thus, the energy can be applied gently to achieve different levels of tissue heating (Lapidoth and Halachmi 2015).

The RF systems can be "monopolar," "bipolar," "multipolar," and "unipolar" (Lapidoth and Halachmi 2015).

Monopolar RF

These devices use an active electrode to apply the RF to the area of treatment, in the form of a handpiece, and a return electrode, usually in the form of a grounding pad with a large contact area, which is placed far from the treatment zone (Fig. 33).

A high RF current density is created at the active electrode, and the current diverges as it penetrates the tissue going toward the large return electrode. Therefore, the heat is generated near the active electrode, and it does not depend on the size, shape, or position of the return electrode.

The RF current diverges rapidly away from the electrode; thus, the heating effect decreases. At a distance equal to the electrode size, heating becomes insignificant. The heat zone can be estimated as half the size of the electrode. Therefore by controlling the RF power and the geometry and size of the electrode, it is possible to control the penetration depth and the effect on the tissue.

Popular monopolar system uses are in surgery for the cutting and coagulation of blood vessels. In dermatology, there is the application for skin tightening and collagen remodeling, as the geometry of the large electrode targets the deeper tissues of the dermis (Fig. 34).

Bipolar RF

This configuration uses two electrodes which are placed close to each other and in contact with the treatment zone. The RF current flows between the electrodes and does not spread to other parts of the body as in the monopolar configuration. This geometry creates a more uniform heating at the treatment zone compared to the monopolar devices (Fig. 35).

Both electrodes create an equal thermal effect near them, and the divergence of the RF current is reduced because of the small distance between them. Therefore, most of the heat is concentrated

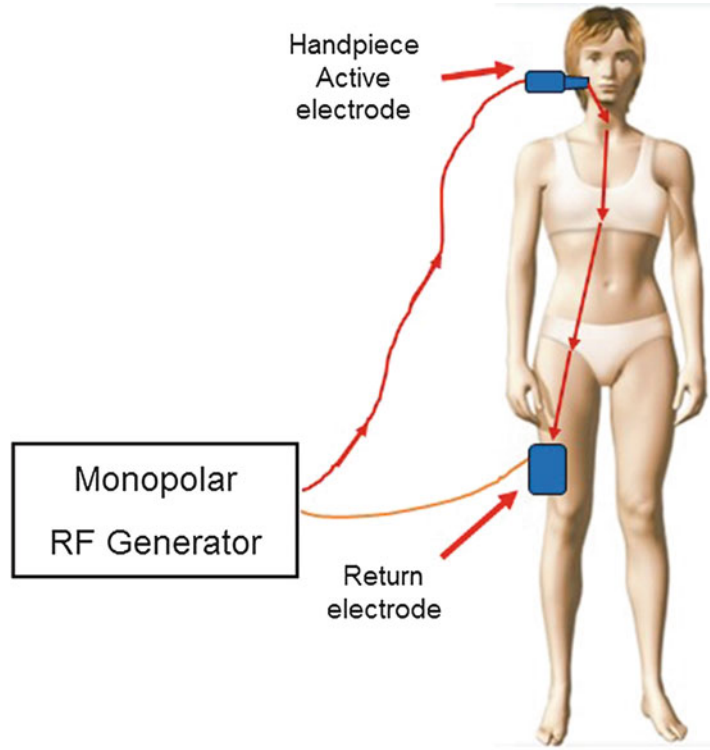

Fig. 33 Basic configuration of a monopolar device

Fig. 34 Example of monopolar device used for skin tightening, Thermage ThermaCool, Solta Medical

Fig. 36 RF + suction, Reaction™ (Viora)

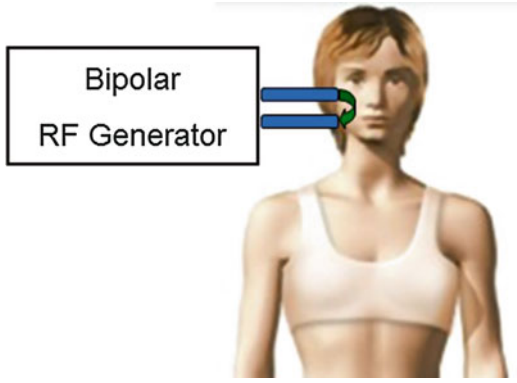

Fig. 35 Schematic of a bipolar RF system

near the electrodes, thus allowing a greater control over the size of the treated volume.

The penetration depth is a function of the size of the electrodes and the distance between them. By increasing the separation of the electrodes, the RF current can go deeper, but the divergence also increases thus reducing the desired heating effect. If the separation is too high compared to the electrode size, the heating profile will be similar to two monopolar electrodes. When the separation of the electrodes is comparable to the size of the electrode, the penetration depth is approximately half of the distance between them (Lapidoth and Halachmi 2015).

The folding of the skin between the electrodes, for example, by applying negative pressure (in the form of vacuum), allows a uniform heating of a large tissue volume that can reach up to a few centimeters. This technique is used in devices for body contouring and cellulite such as Reaction™ of Viora (Fig. 36) and VelaShape™, which uses the electro-optical synergy (ELŌS) technology developed by Syneron Candela, described below.

Multipolar RF

It is an interesting approach to the bipolar RF geometry. In this case, a series of bipolar electrodes are used in a circular or linear configuration. The RF current flows between them, producing a more homogeneous heating effect over a larger tissue volume and variable penetration depths, as shown in Fig. 37. It also quickly reaches the desired treatment end point

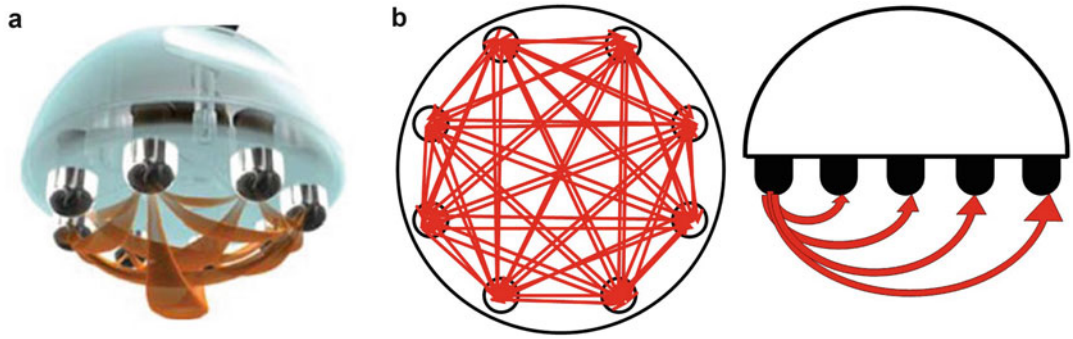

Fig. 37 (**a**) Schematics of a multipolar RF configuration showing RF current flow between electrodes (**b**) at different penetration depths

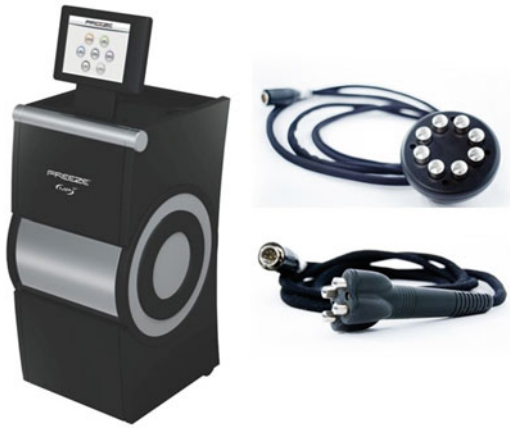

Fig. 38 Freeze™ multipolar RF and its applicators, from Venus Concept

temperature, since more electrodes are used simultaneously (Figs. 37 and 38).

Unipolar RF

This RF configuration uses a single electrode that works, in some ways, as an antenna for electromagnetic energy coupling in the skin. It is different from monopolar RF, which uses one active electrode and one return electrode, and in this case, the RF current flows into the skin (Fig. 39).

The electromagnetic field coupling in human tissue produces heat. The RF heating effect depends on the operating frequency of the

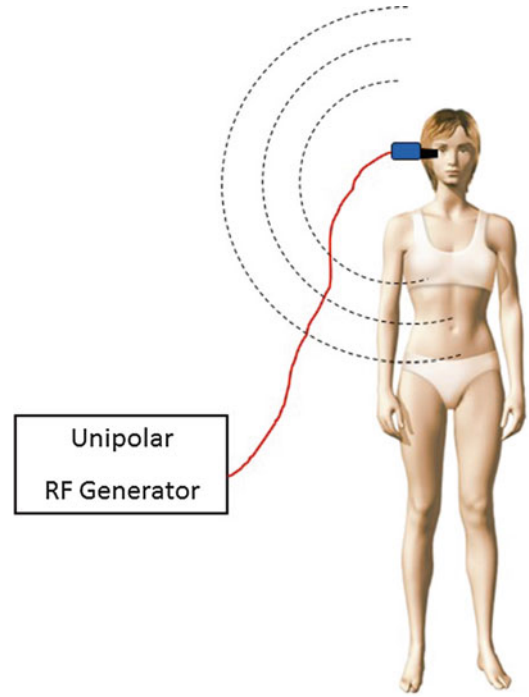

Fig. 39 Schematics of a unipolar RF generator

device. There are two mechanisms of heating biological tissue containing water: ionic current, which is produced by moving charged particles (electrons), and rotation of dipoles of water molecules. These two forms of interaction lead to heating and consequent increase in temperature of the biological tissue (Lapidoth and Halachmi 2015) (Fig. 40).

Fig. 40 The platform Accent Ultra™, from Alma Lasers, with a unipolar handpiece

Fractional RF

Fractional bipolar RF (FRF) was developed following the same concepts and success of fractional lasers as described previously and is gaining great popularity in dermatology. The procedure is based on the heating or ablation of multiple small points in the skin (MTZ), with a spot size of 100–400 μm, leading to improvements in the quality of the skin, wrinkle reduction, and treatment of acne scars and stretch marks (Lapidoth and Halachmi 2015; Brightman et al. 2009; Rongsaard and Rummaneethorn 2014).

The RF has the potential to provide different patterns of energy and heat distribution from the MTZ shape interaction of fractional lasers. In contrast to lasers where the thermal effect is limited to the periphery of the ablation crater (ablative procedure) or the coagulated column (in non-ablative procedures), the RF energy flows through the entire dermis, adding volumetric heating to the fractional treatment. This produces a more effective effect of skin tightening.

There are mainly two types of RF fractional technologies:

1. A matrix of bipolar microelectrodes applying the RF energy from the surface
2. A grid of microneedles which internally deliver the RF energy within the dermis

The surface electrodes provide a more superficial effect improving texture and lines, treating stretch marks and smoothing acne scars. The bipolar RF is applied with a matrix of active microelectrodes as shown in (Fig. 41).

A normal bipolar device, described above, uses a large area electrode and has low power density, and the current and subsequent heating effect is limited to the tissue between the electrodes. In FRF, the active electrode is converted into a series of microelectrodes, which increases the energy density, thus producing an ablation effect near the electrode, and as the energy flows to the large return electrode, it spreads, reducing the effect which is limited to skin coagulation and skin tightening (Fig. 42). This action is similar to a water nozzle. If we approach the nozzle, and the water jet is concentrated, we can become excessively wet. As we move away from the nozzle, the water spreads and only a few drops can reach us (Fig. 42).

An interesting variation of the fractional bipolar RF was developed by Syneron Candela, the "Sublative RF," used in the Matrix RF and eMatrix devices. The proposal is to deliver heat energy to the dermal layer of the skin with minimal epidermal damage. By controlling the RF current energy and delivery pulse, it is possible to correct epidermal defects and promote aggressive remodeling of the deeper dermis. Since the effect on the epidermis is minimal, the recovery time is shorter, and it also reduces the risk of infection and pigmentary changes (Fig. 43).

The RF microneedle approach is based on the introduction of a set of fine dielectric-coated needle electrodes deep into the skin, which is then activated to deliver energy producing a strong dermal remodeling. Since the energy is directly deposited into the deep dermis, there is no effect in the epidermis, which is preserved. Side effects

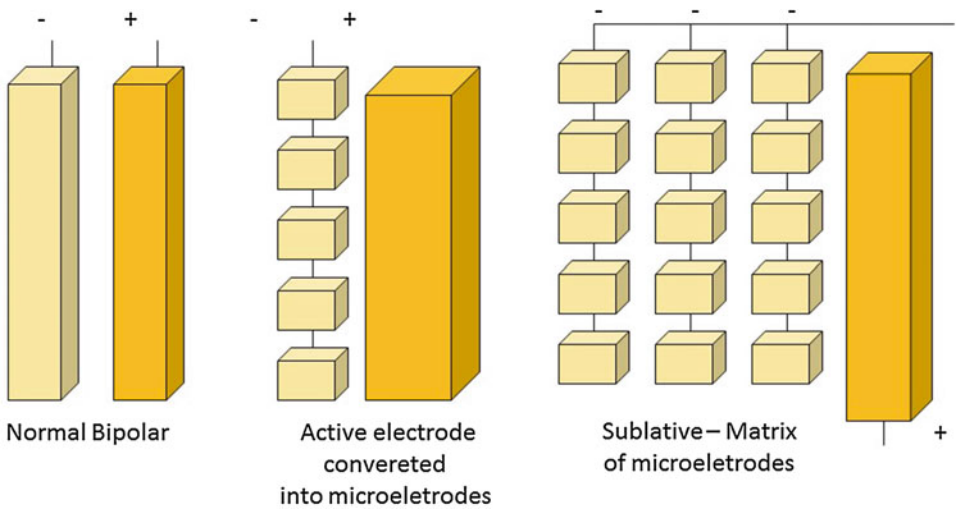

Fig. 41 Schematics of a fractional RF device

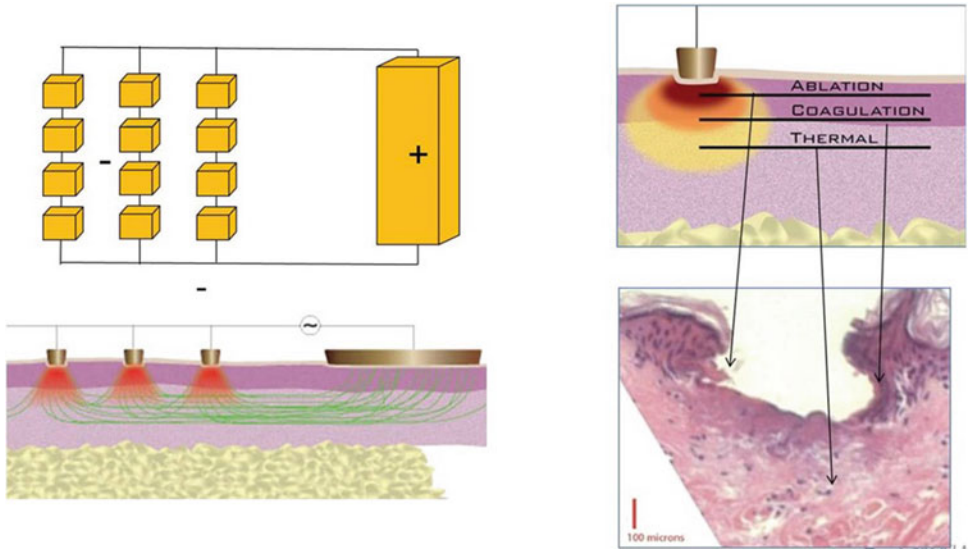

Fig. 42 Impact of the fractional RF in the tissue

and recovery time are minimal. Compared to the surface fractional RF application, microneedles can produce higher temperatures in the deep dermis and therefore stronger collagen contraction, which leads to the improvement of deep wrinkles and skin tightening (Lapidoth and Halachmi 2015).

The RF energy penetration depth is controlled by adjusting the size of the needle, and the effect is confined to the skin between the electrodes (Fig. 44).

The combination of a superficial fractional treatment (Sublative), improving epidermis and collagen remodeling in the upper dermis, with deep dermal remodeling produced by the microneedle device represents a high potential for a complete skin improvement with minimal adverse effects and recovery time.

Fig. 43 The eMatrix™ and the Sublative™ tip, from Syneron Candela

Fig. 44 INFINI™ skin treatment platform, with surface fractional RF and microneedle handpieces, from Lutronics Inc.

It is often said that fractional RF is safe for all skin types because of its "color-blind" characteristic. However, it should be noted that, while the RF interaction with skin does not depend on the presence of melanin or any other chromophore, darker skin types and tanned skin are still susceptible to post-inflammatory hyperpigmentation (PIH). The FRF will heat and induce a wound healing process response in the skin; therefore, it is wise to treat these high-risk skin types with greater caution.

Hybrid Systems

Looking to overcome limitations and to expand the safety and efficacy of treatments with laser or intense pulsed light (IPL) systems, the industry has diversified technology associating light to other forms of energy creating the so-called hybrid systems.

An example of great success of this diversification is the electro-optical synergy (ELŌS™) technology synergy of light with radio frequency (RF) developed by the inventor of the intense pulsed light, Dr. Shimon Eckhouse, in Syneron Candela, Israel (Doshi and Alster 2005; Sadick et al. 2005; Lapidoth et al. 2005; Sadick and Trelles 2005).

The ELŌS™ technology employs a bipolar RF with a water-cooled tip simultaneously with the laser or IPL pulse, as illustrated in Fig. 45.

Following the principle of selective photothermolysis, light heats the chromophore preserving the surrounding tissue. A cool tip protects the surface of the skin and "pushes" the RF to deeper

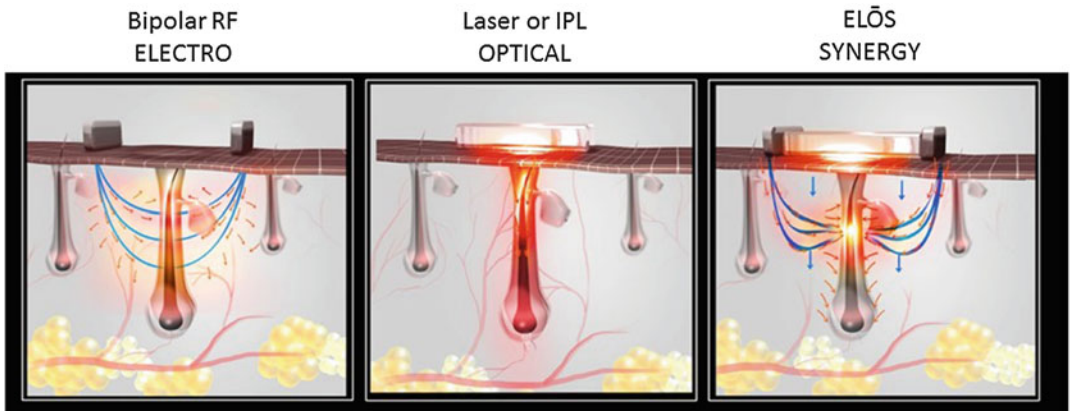

Fig. 45 The ELŌS™ effect, synergy of bipolar RF + light in hair removal

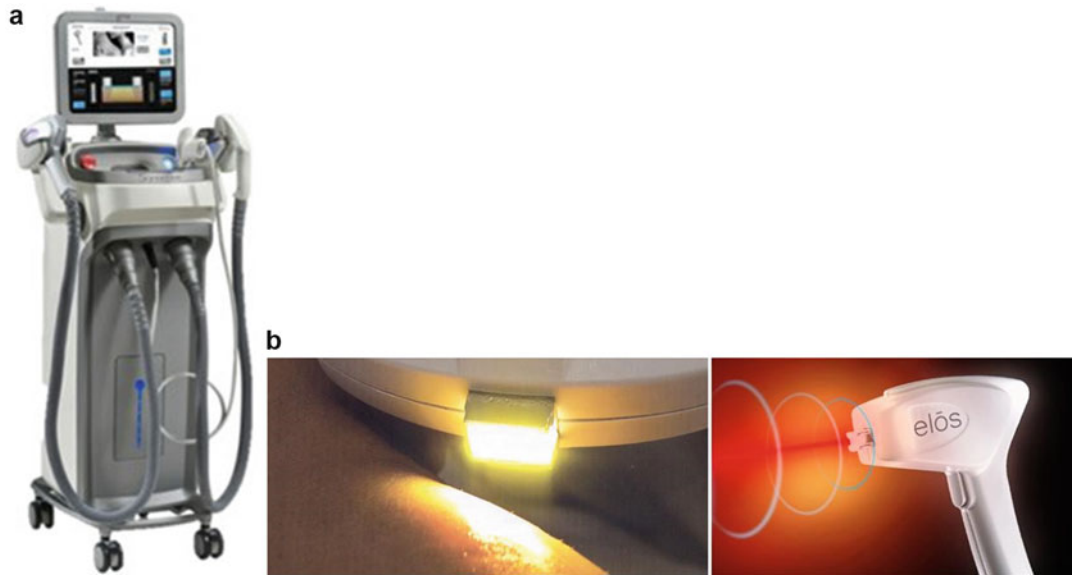

Fig. 46 (**a**) ELŌS plus system, Syneron Candela – multi-platform with several handpieces including laser, IPL, and infrared, all associated with bipolar RF, and a fractional RF. (**b**) ELŌS handpiece showing the bipolar electrodes and the IPL simultaneously

layers. The RF will be concentrated in the heated tissue because it has better conductivity, and this will cause the chromophore to overheat leading to the desired therapeutic effect (Lapidoth and Halachmi 2015).

Figure 45 illustrates this synergic effect in hair removal treatment, but the same occurs in the treatment of pigmented and vascular lesions, skin rejuvenation, and tightening (in which an infrared light source in the range from 700 to 1200 nm is used with bipolar RF) (Figs 46a, b).

The main advantage of the ELŌS™ is the reduced optical fluence needed for the treatment, thus minimizing patient discomfort during the session and increasing safety for darker skin types. Because of the RF action, simultaneous effects such as skin tightening during a treatment of pigmented lesions can also happen.

Fig. 47 ELŌS for circumferential and fat reduction, cellulite treatment, and skin tightening, VelaShape III (Courtesy: Syneron Candela)

Other applications of this technology are circumferential reduction, cellulite treatment, and skin tightening. In this case, bipolar RF is associated with an infrared source, a lamp emitting from 700 to 2,000 nm, or a high-power LED (870 nm), rotating cylinders, which produces massage, drainage, and suction. The cylindrical rollers are the RF electrodes. The suction causes a skinfold, which increases the penetration of the RF and light as explained before (Alster and Tanzi 2005; Wanitphakdeedecha and Manuskiatti 2006; Boechat 2009) (Fig. 47).

The goal is to increase the temperature of (up to 43 °C) deep tissue, which accelerates the metabolism of fat cells and thereby reduces their size leading to circumferential reduction. For a longer exposure time and higher temperature (45 °C), it is possible to produce apoptosis of fat cells since they are more sensitive than skin cells thus reducing localized fat. The effect of skin tightening occurs because of the stretching of elastic fibers and the remodeling of collagen, improving the overall skin quality.

Applications of Laser in Dermatology

Laser for Vascular Lesions

Vascular lesions have been some of the most frequently treated skin conditions since the advent of lasers. The flash-lamp-pumped pulsed dye laser (PDL) has a wavelength between 585 and 600 nm and is used to treat superficial blood vessels, as these wavelengths coincide with the absorption peaks of oxyhemoglobin (Anderson and Parrish 1983; Spicer and Goldberg 1996). Vascular-specific laser systems target intravascular oxyhemoglobin leading to the destruction of various congenital and acquired vascular lesions. Three main absorption peaks for oxyhemoglobin are within the visible range of the electromagnetic spectrum: 418, 542, and 577 nm. Lasers that have been used to treat vascular lesions include the argon (488–514 nm), argon-dye laser (577 and 585 nm), KTP (532 nm), krypton (568 nm), copper vapor/bromide (578 nm), PDL (585–595 nm), and Nd:YAG (532 and 1,064 nm) (Anderson and Parrish 1983; Spicer and Goldberg 1996; Osorio and Torezan 2009; Tanzi et al. 2003a). At 577 nm, the PDL penetrates the skin to a depth of 0.5 mm, 0.2 mm below the dermoepidermal junction, for treatment of dermal vascular lesions. Penetration can be further increased to 1.2 mm if the wavelength is changed to 585 nm. At this longer wavelength, less light is absorbed by melanin. Therefore, the risks of depigmentation are decreased (Tanzi et al. 2003a).

Purpura-inducing effect of the PDL in the treatment of capillary malformations is one of the most common side effects observed (Dover et al. 1995). In general, the smaller the pulse duration, the more explosively energy is delivered and the more likely it is to induce purpura. The classic short pulse duration (0.45–1.5 ms) that ruptures small vessels is still the most effective pulse duration for treating capillary malformations, with the expected purpura as a clinical end point. With a pulse duration (450 μs) shorter than the thermal relaxation time (TRT) of small- to medium-sized blood vessels (1 ms), the PDL respects the principles of selective photothermolysis leading to selective vascular injury avoiding thermal damage

to the surrounding tissue. On the other hand, longer pulse durations coagulate the blood vessels and do not induce purpura (Anderson and Parrish 1983; Tanzi et al. 2003a; Dover et al. 1995). Diffuse erythema of the face and more superficial telangiectases may benefit from the sub-purpuric parameters. Due to the low-risk profile, PDL has been used to treat a variety of vascular lesions such as port-wine stains, facial telangiectases, hemangiomas, pyogenic granulomas, Kaposi's sarcoma, and poikiloderma of Civatte (Tanzi et al. 2003a; Dover et al. 1995; Tan et al. 1989; Reyes and Geronemus 1990; Ashinoff and Geronemus 1991; Alster and Wilson 1994; Fitzpatrick et al. 1994; Kauvar and Geronemus 1995).

The Nd:YAG laser has a wavelength of 1,064 nm, which can also be used in the treatment of vascular lesions. This longer wavelength corresponds to the optical window that enables deeper penetration into the dermis to target larger vessels and is less likely to produce bleeding. However, it is important to emphasize that at 1,064 nm, there is more penetration into the skin but less absorption by hemoglobin. Therefore, melanin and water may act as competing chromophores (Osorio and Torezan 2009; Tanzi et al. 2003a; Stewart et al. 2013). High-energy settings or absence of a cooling device can cause bulk heating, resulting in burns and scarring. Generally, 1,064 nm Nd:YAG laser is used to treat larger vessels, such as larger capillaries malformations and venules of the face and limbs, as well as bluish vascular lesions such as venous lakes. The double-frequency Nd:YAG laser – KTP laser – (by halving the 1,064–532 nm when the beam passes through a KTP crystal) is currently used to treat very superficial facial telangiectases as it closely matches one of the most superficial hemoglobin absorption peaks (Tanzi et al. 2003a; Stewart et al. 2013). Compared with longer wavelength vascular-specific lasers, potential limitations of the 532-nm wavelength include decreased tissue penetration of its shorter wavelength resulting in diminished absorption by deeper vessels. In addition, the 532-nm wavelength is more absorbed by melanin than PDL, which may limit its use for patients with darker skin types.

The other abovementioned krypton, argon, argon-dye, copper vapor/bromide, and some KTP devices are continuous or semicontinuous (quasi-CW) lasers that are used to treat cutaneous vascular conditions such as rosacea, poikiloderma of Civatte, and port-wine stains. These devices are not pulsed systems and consequently they offer higher risks of thermal damage to the surrounding skin. Thus, using continuous or quasi-CW lasers is often associated with higher incidences of hypertrophic scarring and textural changes than is seen with pulsed laser systems (Tanzi et al. 2003a; Stewart et al. 2013; Apfelberg 1980).

Laser for Pigmented Lesions

The major endogenous pigment of clinical importance is melanin, whereas tattoo ink (amateur, professional, iatrogenic, or traumatic) is the most commonly targeted exogenous pigment. Melanin does not have any especific absorption peak. However, it increasingly absorbs shorter wavelengths of light below about 1,000 nm. Therefore, a multitude of laser wavelengths can be used to target melanin, although none is entirely specific for this chromophore: 532 nm Nd:YAG KTP, 595 nm PDL, 694 nm ruby, 755 nm alexandrite, and 10,640 nm Nd:YAG (Anderson and Parrish 1983; Osorio and Torezan 2009; Goldberg 1993).

Melanin-specific, high-energy, QS laser systems can successfully lighten or eradicate a variety of benign epidermal and dermal pigmented lesions and tattoos with minimal risk of untoward effects. Epidermal lesions (solar lentigines, ephelides, cafe'-au-lait macules, and seborrheic keratoses), dermal and mixed epidermal/dermal lesions (melanocytic nevi, blue nevi, nevi of Ota/Ito, infraorbital hyperpigmentation, Becker's nevi, and nevus spilus), and tattoo pigment area all are suitable to QS laser treatment (Chang et al. 1996; Shimbashi et al. 1997; Yang et al. 1996; Ono and Tateshita 1998; Osorio and Torezan 2009; Tanzi et al. 2003a; Stewart et al. 2013; Grevelink et al. 1997b; Ueda and Imayama 1997; Kunachak et al. 1999; Alster and Williams 1995). Melasma, which is considered one of the most difficult-to-treat skin diseases, may benefit

from QS lasers at very low fluences and high repetition rates, targeting the melanosome with minimal surrounding inflammatory process. In this case, many treatment sessions performed weekly are necessary to achieve the best results, although not long-lasting in the authors' experience (Jeong et al. 2008; Mun et al. 2010).

Based on Anderson and Parrish's principle of selective photothermolysis, QS laser systems replaced earlier CW lasers as a result of their ability to induce thermal necrosis that remains largely confined to the melanosomes with limited spread of coagulative necrosis to surrounding structures (Anderson and Parrish 1983; Rongsaard and Rummaneethorn 2014). Before the QS lasers' advent, the continuous and quasi-CW laser systems have been used for pigment and tattoo destruction. These lasers typically emit light with pulse durations longer than the thermal relaxation time of a melanosome and, therefore, may result in scarring or textural irregularities as a result of excessive thermal damage of surrounding tissue during laser irradiation. Therefore, the use of CW lasers is reserved for removal of epidermal lesions because treatment of deeper, dermal lesions is often associated with significant tissue scarring (Osorio and Torezan 2009; Tanzi et al. 2003a; Stewart et al. 2013).

The QS laser produces high-energy nanosecond pulses in the green to near-infrared spectrum that selectively target melanin or ink and are less likely to cause adverse effects (Raulin et al. 1998). The wavelengths of the Q-switched ruby (694 nm), alexandrite (755 nm), and double-frequency Nd:YAG (532 nm) lasers are the most commonly used. The QS 1,064 Nd:YAG laser penetrates deeper into the skin, becoming suitable for the treatment of deeper pigmented lesions and darker-skinned individuals (Raulin et al. 1998; Tanzi et al. 2003a; Stewart et al. 2013; Apfelberg 1980; Goldberg 1993; Ashinoff and Geronemus 1992).

Superficial pigment is best treated with short wavelength lasers, whereas deeper pigment responds better to long wavelengths with a greater penetration. Dark-skinned patients are more safely treated with long-wavelength lasers, preventing the superficial uptake of laser energy by epidermal melanosomes and thus reducing the potential depigmentation (Osorio and Torezan 2009; Tanzi et al. 2003a).

With the development of QS laser technology, tattoo removal has become much safer (Osorio and Torezan 2009; Tanzi et al. 2003a; Goldberg 1993; Ashinoff and Geronemus 1992; Kilmer and Garden 2000; Haedersdal et al. 1996). For optimal pigment removal, the choice of laser is based on the absorption spectra of the ink colors present within the tattoo. Black pigments absorb throughout the red and infrared spectrum and can be treated with QS ruby (694 nm), QS alexandrite (755 nm), or QS Nd:YAG (1,064 nm) lasers. Blue and green inks are targeted in the 600- to 800-nm range, thus making the ruby or alexandrite laser the most appropriate choice. Red, orange, and yellow tattoo inks are specifically destroyed by green light, rendering the 532-nm QS Nd:YAG laser or 510-nm PDL the optimal treatment for these colors. It is important to emphasize that QS lasers may also be used as long-pulse lasers, in the millisecond pulse domain width (Kilmer and Garden 2000; Haedersdal et al. 1996; Reid et al. 1983; Taylor et al. 1990; Kilmer and Anderson 1993; Fitzpatrick et al. 1993). Therefore, in the long-pulse mode, they cannot adequately and safely target small-diameter melanosomes or ink particles. Competing chromophores within skin structures, such as capillaries, present greater relevance with long-pulse-width lasers. Long-pulse lasers can target larger structures such as clusters of lentiginous melanocytes or pigmented hair shafts and can be useful for hair removal (Campos et al. 2000; Eremia et al. 2001; Dierickx et al. 1998; Grossman et al. 1996).

The most common side effects are punctate bleeding, edema, pruritus, vesiculation and blistering, purpura, hypopigmentation or hyperpigmentation, scarring, permanent hair loss, and systemic allergic or localized granulomatous reactions to disrupted tattoo ink particles. Some of these side effects are more prone in dark-skinned individuals due to the increased absorption by surrounding melanin (Tanzi et al. 2003a; Stewart et al. 2013).

Recently, the development of new QS lasers 755 nm and 1,064 nm which operate in picosecond

domain resulted in more specific damage confined to the tattoo particle. Optimal selective photothermolysis of a pigment particle requires pulse durations equal to or less than the particle's thermal relaxation time. Since tattoo particles in skin range in diameter from 40 to 300 nm, picosecond pulses would approximate TRT more closely and, therefore, might be more effective at tattoo particle fragmentation (Freedman et al. 2014; Ibrahimi et al. 2013).

Resurfacing: Ablative Technology

Cutaneous laser resurfacing represents a major advance in the treatment of photodamaged facial skin and atrophic scarring. With recent advances in laser technology, especially with the advent of fractional ablative systems, this procedure has become widely accepted as an effective means for facial rejuvenation (Stewart et al. 2013).

Ablative lasers are generally used to resurface and rejuvenate the skin by treating rhytides and scars. The first continuous carbon dioxide laser emits a beam of far-infrared radiation at 10,600 nm, mainly targeting water. The CW-CO_2 laser does not conform to the principle of selective photothermolysis and thus induces more depigmentation and scarring (Rongsaard and Rummaneethorn 2014; Waldorf et al. 1995; Alster and Garg 1996). However, this technology is still used as a relatively bloodless skin incision tool, but for resurfacing purposes has given way to high-energy and pulsed CO_2 laser. These newer systems are able to effect controlled tissue ablation with limited coagulative necrosis of unintended neighboring structures. Because of its flexibility and low side-effect profile, the high-energy, pulsed, and scanned CO_2 laser has been considered the gold standard for facial rejuvenation (Waldorf et al. 1995; Alster and Garg 1996; Fitzpatrick et al. 1996; Apfelberg 1997; Ross et al. 1999a; Dover et al. 2000). Ablation is defined as rapid cellular heating and instant tissue vaporization and can remove 20–60 mm of the skin surface after a single pass. Additionally to the ablated layer, a zone of collateral thermal damage (200 to 300-μm) occurs as a consequence of heat diffusion (Ross et al. 1999a; Dover et al. 2000). The tissue coagulation and protein denaturation lead to hemostasis and collagen remodeling. The latter may take up to several months to achieve its maximal effect, but the resulting improvement in rhytides and scarring is significant (Tanzi et al. 2003a; Fitzpatrick et al. 1996; Apfelberg 1997; Ross et al. 1999a; Dover et al. 2000; Fitzpatrick 2002). Besides the excellent final outcome for skin rejuvenation, the incidence of side effects was considered potentially high, including infection, pain, prolonged erythema, milia, scarring, permanent late hypopigmentation, and demarcation lines between treated and non-treated skin (Fitzpatrick 2002; Alam and Warycha 2011).

The short-pulsed 2,940-nm Er:YAG laser was developed subsequent to the CO_2 laser in an attempt to emulate some of its beneficial effects while limiting its side-effect profile and morbidity (Stewart et al. 2013; Goldman et al. 1999). The Er:YAG laser has a higher absorption coefficient than that of the CO_2 laser. Because 90% of the epidermis is composed of water, most of the energy of the erbium laser is superficially absorbed. The erbium laser can, therefore, effect fine tissue ablation, penetrating to an average depth of 2–5 μm per J/cm^2 with zones of thermal necrosis extending another 10–15 μm. Collateral thermal damage is reduced and minimal vascular coagulation is effected, leading to inefficient hemostasis during treatment (Osorio and Torezan 2009; Tanzi et al. 2003a). The limited thermal damage also accounts for the less pronounced clinical improvement typically seen after with CO_2 laser. Another ablative wavelength, 2,790 nm, gave rise to the erbium-doped yttrium scandium gallium garnet laser (YSGG) (Er:YSGG) (Stewart et al. 2013). Besides the improvement of skin aging, other well-known indications of ablative lasers are removal of benign epidermal and dermal lesions such as seborrheic keratoses, verruca vulgaris, xanthelasma, and sebaceous gland hyperplasia and adnexal tumors such as syringoma and trichoepithelioma; treatment of premalignant and malignant skin lesions, including actinic cheilitis, superficial basal cell carcinoma, and squamous cell carcinoma in situ has been reported (Spicer and Goldberg 1996; Osorio and Torezan 2009; Tanzi et al. 2003a; Stewart et al. 2013). The CO_2 laser can also be used for

excisional and incisional operations, including blepharoplasty or rhytidectomy, with the advantage of the near-bloodless field created from the CO_2 laser-tissue interaction, effecting minimal postoperative edema or bleeding (Ross et al. 1999a; Dover et al. 2000; Fitzpatrick 2002).

Resurfacing: Non-ablative Technology

Non-ablative resurfacing lasers preserve the epidermis either relatively or absolutely while still allowing bulk heating and denaturation of the dermal proteins. As a consequence, they allow for the beneficial effects of tissue remodeling and skin tightening with decreased recovery time and lower risk of scarring, depigmentation, and infection (Tanzi et al. 2003a; Bjerring et al. 2000).

Non-ablative laser used today emits light within the infrared portion of the electromagnetic spectrum (1,000–1,600 nm), along with other modalities such as RF, focused ultrasound, and IPL, which have all been used as non-ablative resurfacing therapies (Stewart et al. 2013; Alexiades-Armenakas et al. 2008; Zelickson et al. 1999). Specific lasers for dermal targets such as hemoglobin and deeper melanin are non-ablative lasers, but in current nomenclature, non-ablative lasers are those that target dermal water while preserving the same target, water, in the epidermis. At these wavelengths (1,000–1,600 nm), absorption by superficial water-containing tissue is relatively weak, thereby effecting deeper tissue penetration. Non-ablative laser resurfacing induces collagen remodeling by creation of a dermal wound without damaging the epidermis (Tanzi et al. 2003a; Levy et al. 2001, 2002; Trelles et al. 2001; Goldberg and Metzler 1999; Goldberg and Whitworth 1997b; Rostan et al. 2001; Tanzi et al. 2003b). Contact and dynamic cooling devices are used simultaneously with laser irradiation to ensure epidermal preservation. The classical non-ablative lasers are not capable of results comparable with those of ablative laser systems and have shown to improve mild to moderate atrophic scars and rhytides with virtually no external wound. Non-ablative laser resurfacing is ideal for patients with either mild cutaneous photoaging (Alexiades-Armenakas et al. 2008; Zelickson et al. 1999; Levy et al. 2001, 2002; Trelles et al. 2001; Goldberg and Metzler 1999; Goldberg and Whitworth 1997b; Rostan et al. 2001; Tanzi et al. 2003b). In addition, the results may differ between individuals, multiple treatments are necessary, and maintenance with repeat treatments is required. In practice, the results achieved with these laser devices are far from being reasonable, and they are no longer routinely offered to patients (Waldorf et al. 1995; Tanzi et al. 2003b; Levy et al. 2002).

Fractionated Lasers

The introduction of fractionated lasers in 2004, by Manstein et al., represented the beginning of a new era in the application of laser technologies in dermatology. Initially, the fractionated systems covered the non-ablative wavelengths, specifically 1,550 nm (Manstein et al. 2004). These devices rely on high-fluence irradiation to form multiple, discrete vertical zones of thermal damage with completely spared intervening areas. These microthermal zones (MTZ) may vary in depth and width depending on the levels of energy and density set. The MTZ are separated by uninvolved tissue (accounting for up to 75–85% of the treated surface area), which act as a reservoir for tissue regeneration by providing nutritional support and an intact microstructure for keratinocyte and fibroblast migration (Manstein et al. 2004; Manstein and Laubach 2011).

Fractionated lasers can be either non-ablative or ablative. In general, the fractional ablative devices are more effective but tend to have longer recovery time than the fractional non-ablative devices. Non-ablative devices (Nd:YAG, Er:glass, Er:fiber, and Er:thulium) have wavelengths of between 1,320 and 1,927 nm, while the ablatives (Er:YAG, Er:YSGG, and CO_2) have longer wavelengths between 2,940 and 10,600 nm (Manstein et al. 2004; Geronemus 2006; Manstein and Laubach 2011).

The most widely known and extensively evaluated fractionated laser, the 1,550 nm Er:glass, typically produces erythema and edema lasting 2–3 days post-procedure. However, this non-ablative laser usually requires multiple sessions and may only show modest improvements in rhytides and skin tightening when compared with the ablative CO_2 (Manstein et al. 2004; Manstein and Laubach 2011). Besides this, fractional non-ablative lasers provide good results for photoaging, acne scars, and stretch marks, with little downtime and relatively safe profile. The side effect profile of these lasers was greatly improved, with pinpoint bleeding generally lasting less than 24 h and moderate erythema lasting only 1 week. However, high-setting parameters of these lasers can produce prolonged erythema and more complications such as scars, ulceration, and depigmentation (Stewart et al. 2013; Ramsdaell 2012).

The non-ablative fractionated devices progressed to ablative fractionated versions of Erb:YAG 2,940 nm and CO_2 10,600 nm to produce results approaching those seen with the non-fractional ablative CO_2 laser. Considering their high efficacy and lower incidence of side effects (compared to the non-fractional ablative lasers), these systems are now considered by many to be the gold standard in skin resurfacing (Manstein and Laubach 2011; Tierney et al. 2012).

Photoepilation

Lasers and IPL sources with wavelengths in the red or near-infrared region (600–1,200 nm) are most often used for hair removal because they effectively target melanin within the hair shaft, hair follicle epithelium, and heavily pigmented matrix (Campos et al. 2000; Eremia et al. 2001; Dierickx et al. 1998; Grossman et al. 1996). Furthermore, devices operating within this region of the electromagnetic spectrum can penetrate to the appropriate depth of the dermis because they are within an "optical window" in which selective absorption by melanin is coupled with deep penetration of laser energy (Campos et al. 2000). However, the presence of melanin within the epidermis represents a competing site for laser energy absorption. Therefore, active cooling must be used to minimize epidermal injury, especially in darker skin types (Lasers Surg et al. 1997; Nanni and Alster 1998).

Laser-tissue interactions that occur within the melanin-rich matrix and hair shaft heat the surrounding follicle. To limit the thermal damage, the pulse duration should be shorter or equal to the thermal relaxation time of the hair follicle estimated to be approximately 10–100 ms, depending on the diameter of the follicle (Lasers Surg et al. 1997; Nanni and Alster 1998; Ross et al. 1999b; Dierickx 2002). Thus, most systems currently used for long-term hair reduction provide pulse durations in the millisecond domain. However, other components of the follicular unit, such as follicular stem cells, do not contain significant amounts of melanin and may be located some distance from the targeted pigmented structures.

Laser systems and IPL sources currently used for the reduction of hair include the long-pulse (LP) ruby (694 nm), LP alexandrite (755 nm), pulsed diode (800 nm), QS and LP Nd:YAG (1,064 nm) lasers, and IPL (590–1,200 nm) sources (Nanni and Alster 1998; Ross et al. 1999b; Dierickx 2002; Gold et al. 1997). The longer the wavelength, the higher the penetration into the skin and the safer it becomes for dark-skinned individuals. So for dark skin types, it is preferable to use a 800 or 1,064 nm laser system instead of a 694 nm, which will be also absorbed by the epidermal melanin, thus leading to more depigmentation (Campos et al. 2000; Dierickx et al. 1998; Nanni and Alster 1998).

Other components of the follicular unit, such as follicular stem cells, do not contain significant amounts of melanin and may be located some distance from the targeted pigmented structures. Recently, it has been proposed that pulse durations longer than the TRT of the shaft may be more appropriate to induce permanent hair reduction. In contrast to the original theory of selective photothermolysis, the extended theory proposes that the target be destroyed by heat diffusion from the

pigmented area to the target rather than by direct heating. Preliminary studies demonstrate super-pulse heating of the follicle with a pulse duration longer than 100 ms has resulted in long-term hair reduction without adverse sequelae (Stewart et al. 2013; Ross et al. 1999b).

Side effects are rare and may include blistering, fine epidermal crusting, purpura, and transient hyperpigmentation or hypopigmentation. Patients at highest risk of complications are those with recent sun exposure or darker skin types (Campos et al. 2000; Dierickx et al. 1998; Alam and Warycha 2011).

IPL sources emitting wavelengths ranging from 550 to 1,200 nm can also be used to effect hair reduction. By using a series of cutoff filters, a specific wavelength may be selected to suit an individual skin type and color. As well as with lasers, IPL requires multiple treatment sessions to result in a considerable hair reduction. Side effects and complications of IPL treatment are similar to those seen after laser-assisted hair removal and include rare instances of blistering, crusting, and transient depigmentation (Dierickx 2002; Gold et al. 1997).

Intense Pulsed Light Systems

As with lasers, IPL devices have been used to treat vascular lesions, dyschromia, unwanted hair, acne, and sebaceous hyperplasia. Cutoff filters allow the emission of longer wavelengths, which reduce relative absorption by melanin, protecting darker skin types and relatively increasing nonspecific absorption by water (Weiss et al. 2011). IPL is primarily indicated for targeting melanin and hemoglobin and works best for treating colored chromophores rather than texture. Appropriate filters (560–590 nm) selectively emit light that correspond to the absorption peaks of hemoglobin, thus targeting vascular structures in a manner analogous to the theory of selective photothermolysis (Babilas et al. 2010).

It has been used to successfully treat a variety of vascular lesions including facial telangiectases, port-wine stains, and hemangiomas (Osorio and Torezan 2009; Tanzi et al. 2003a; Weiss et al. 2011). Filters are used to eliminate shorter wavelengths, thereby concentrating light energy so that improved dermal penetration is achieved. Light is delivered as a series of pulse sequences with pulse durations of 2–25 ms and delays between pulses ranging from 10 to 500 ms (Babilas et al. 2010). Because shorter-wavelength light interacts more readily with epidermal melanin, the lower cutoff filters should only be used in patients with fair skin types. With longer pulse durations, the IPL source can slowly heat more deeply located vessels, thus improving treatment efficacy and decreasing the risk of postoperative purpura and hyperpigmentation, but caution is necessary to avoid such side effects. Larger caliber vessels respond well to these treatments because high-energy densities can be delivered by trains of pulses with relatively long delays (40–60 ms) between each pulse (Tanzi et al. 2003a; Stewart et al. 2013). IPL sources emitting wavelengths ranging from 550 to 1,200 nm can also be used to effect hair reduction. By using a series of cutoff filters, a specific wavelength may be selected to suit an individual skin type and color (Dierickx 2002; Gold et al. 1997).

Adverse effects may include purpura, swelling, blistering, inappropriate photoepilation, burns or scarring (darker skin types or sun-tanned skin), demarcation lines, and depigmentation.

Radio Frequency

RF treatments are an alternative to lasers and can be used as monotherapy or as adjuvant therapy with fractional lasers. Three major types of RF treatments exist: unipolar, bipolar, and fractional (Stewart et al. 2013). The most basic is the unipolar/monopolar RF device that uses a single electrode and a grounding pad on the skin. This RF modality offers deeper penetration of the dermis but increased pain and discomfort to the patient. Bipolar RF offers an alternative to unipolar/monopolar RF that can deliver a more focused current to the dermis with less pain due to the need to use lower amounts of energy. Fractional RF uses an array of electrodes that allows for zones of thermal

wounds to be made between areas of unaffected zones, thus stimulating dermal remodeling and allowing for a supply of reservoir cells to promote healing (Brightman et al. 2009). Variations of fractional RF employ microneedles to deliver electrical current to a particular depth within the dermis that decreases damage to the epidermis. Furthermore, there are alternative modalities such as electro-optical synergy systems that combine RF and lasers. The pretreatment with a non-ablative laser lowers the tissue impedance (resistance to flow of current) in the skin to allow deeper penetration of the RFs, decreased level of pain, and reduced amount of RF energy to reach the optimal thermal dose, thus decreasing side effects to the surrounding dermis (Brightman et al. 2009).

The use of RF devices is based on the Ohm's law (Boechat 2009). When volumetric heat of the dermis and subdermal tissue occurs after electrical field interaction with the tissue's natural electrical resistance, the final result is collagen contraction and remodeling, leading to the desired clinical end point of skin tightening. Increased localized blood flow and improved lipolysis are thought to account for the beneficial effects seen in the treatment of cellulite, as least in theory. The epidermis is spared from thermal damage by contact cooling. The main indications of RF are skin laxity, acne scars, and photoaging skin (Osorio and Torezan 2009; Stewart et al. 2013).

The procedure produces significant discomfort and is time-consuming, and the results were somewhat unimpressive and inconsistent in the past. However, advances in handpiece design together with the use of bipolar (or multipolar) RF appears to have increased efficacy, while multiple passes at lower settings have increased patients' tolerance (Boechat 2009). Side effects are low, with transient erythema and edema commonly occurring. Blistering, scarring, and contour changes may be observed after aggressive treatments. Overall, the efficacy of this non-ablative technique remains modest when used as a monotherapy. RF can be used in combination with other modalities such as IPL and laser to produce more significant clinical improvements (Stewart et al. 2013).

Focused Ultrasound

First approved for eyebrow lifting in 2009, high-intensity focused ultrasound (HIFU) has subsequently been trialed in other body regions for the treatment of skin and tissue laxity. Ultrasonic energy is used to achieve precise micro-coagulation zones (coagulative necrosis) deep in the dermis, subcutaneous tissue, and superficial aponeurotic system (Laubach et al. 2008). In HIFU therapy, ultrasound beams are focused on the tissue, and due to the significant energy deposition at the focus, temperature within the tissue can rise to levels from 65 to 85 °C, destroying the diseased tissue by coagulation necrosis. Higher temperature levels are typically avoided to prevent boiling of liquids inside the tissue. Each sonication of the beams theoretically treats a precisely defined portion of the targeted tissue, although in practice cold spots (caused by, among other things, blood perfusion in the tissue), beam distortion, and beam mis-registration are impediments to finely controlled treatments. Tissue damage occurs as a function of both the temperature to which the tissue is heated and how long the tissue is exposed to this heat level in a metric referred to as "thermal dose" (Laubach et al. 2008; Weiss 2012). At high enough acoustic intensities, cavitation can occur. Microbubbles produced in the field oscillate and grow and can eventually implode. During inertial cavitation, very high temperatures inside the bubbles occur, and the collapse is associated with a shock wave that can mechanically damage tissue. HIFU can be used for body contouring (so-called noninvasive liposuction) and skin laxity or applied even in treatment of cancer to destroy solid tumors of the bone, brain, breast, liver, pancreas, rectum, kidney, testes, and prostate (Laubach et al. 2008; Weiss 2012; Solish et al. 2012).

Following treatment, repair of the deep tissue damage leads to contraction and tissue remodeling, resulting in the desired aesthetic effect of reduced skin laxity. The superficial dermis and collateral tissues are spared, which not only limits scarring and downtime but potentially permits HIFU to be used in darker skin types (Laubach et al. 2008; Weiss 2012). However, as with the use of RF,

interindividual variation in response to HIFU treatment is significant.

Conclusion

Laser and intense pulsed light systems are pure light sources with important properties, which allow us to treat accurately and selectively different types of tissue damage, preserving the surrounding healthy tissue. Synergy with radio frequency shows how this equipment can still evolve becoming safer and more efficient. With the advent of fractional skin treatment, a new horizon of applications that are at the same time gentle and effective have emerged in dermatology.

In many applications, light appears as the only effective solution, as in the case of flat vascular lesions in the face or port-wine stains. It has brought a rapid and long-lasting result for unwanted hair removal, the treatment of pigmented lesions, and tattoo removal. It is used in skin tightening, cellulite treatment, circumferential reduction, and localized fat reduction. In a number of applications in dermatology, light emerges as an important complement to the existing techniques, as is the case of rhytidectomy in plastic surgery. It also improves body areas that normally are not treated by surgery, such as the neck, chest, hands, and arms using ablative or non-ablative fractional lasers.

The future will certainly bring more efficient and compact devices. We will have a wider range of applications and, among them, the development of lasers that have the ability to act at the cellular level, stimulating the production of enzymes, which have the purpose of preventing skin aging and skin cancer. Systems that have the subdermal fat as chromophore can open a new horizon of applications for circumferential reduction, cellulite treatment, and improved skin quality. The diagnostic medicine will also benefit from this development.

The more we study about the effects of the interaction of light with living tissue, the more we learn on how to appreciate the variety and complexity of these critical interactions. The result will certainly open doors to a large number of remarkable applications in the following years.

We only have to “tune in” with the energy of light!

Take-Home Messages

1. Laser light is by definition monochromatic, coherent, collimated, and high power, while IPL systems are polychromatic and incoherent.
2. Selective photothermolysis combines pulse duration, wavelength, and fluence to obtain the desired effect on the target, preserving adjacent tissue.
3. Superficial benign pigmented lesions can be treated with Q-switched lasers alexandrite, ruby, or double-frequency Nd:YAG, but also IPL devices can be employed.
4. Fractionated lasers use very high-fluence irradiation to form multiple discrete vertical zones of thermal damage sparing tissue between them. This allows a faster healing time of the treated area.

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Transepidermal Drug Delivery

Maria Claudia Almeida Issa, Gabriela Casabona, Paulo Santos Torreão, and Livia Roale

Abstract

The stratum corneum acts as a barrier that limits the penetration of substances through the skin. Transepidermal drug delivery has been developed to increase the penetration of drugs through the superficial layers of the skin. There are many reports about ablative fractional resurfacing creating vertical channels that assist the delivery of topically applied drugs into the skin. The use of nonablative lasers as well as microneedling technique has been reported with the same purpose. In this chapter we are going to discuss some techniques, mechanism of action, and indications.

Keywords

Skin drug administration • Percutaneous drug administration • Transdermal drug administration • Transcutaneous administration • Transepidermal drug delivery • Transdermal drug delivery

Contents

Introduction

The skin is almost impermeable for most hydrophilic and charged molecules. A molecular weight (MW) of 500 Da is generally accepted as the upper limit for passive diffusion of lipophilic molecules (Haak et al. 2012). Over the years many technologies have been developed to increase

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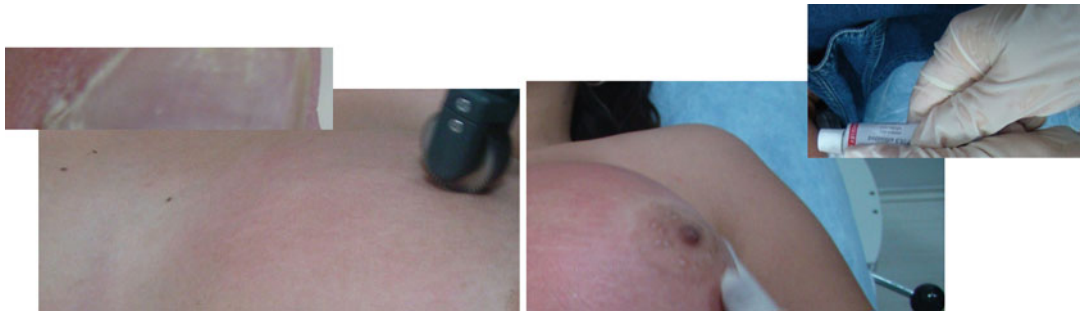

Fig. 1 TED for stretch marks treatment – first step, promoting microchannels with an ablative method (RF), and second step, applying drug (retinoic acid 0.05 % cream) topically on the skin surface

the penetration of drugs through the superficial layers of the skin. These technologies include iontophoresis (Curdy et al. 2001; Li et al. 2002), electroporation (Prausnitz 1999; Vanbever and Préat 1999), photomechanical waves (Lee et al. 1999, 2001), and microneedling (McAllister et al. 2000; Henry et al. 1998). The use of ultrasound (US) for transepidermal administration of different molecules such as insulin, mannitol, glucose, heparin, morphine, caffeine, and lidocaine (Lavon and Kost 2004), both in vitro and in vivo, has been described in the literature. Tachibana and cols (Tachibana and Tachibana 1991) reported that the use of low-frequency ultrasound increases transepidermal transport of insulin through the skin of diabetic rats.

Transepidermal drug delivery (TED) is a novel treatment strategy for dermatology. This technique is based on using a fractioned ablative laser on the skin surface to create microchannels on epidermis to assist the drug topically applied. The standard protocol for TED was developed with fractioned ablative lasers, such as Erbium: YAG and CO_2 lasers. Despite of that, nonablative lasers and microneedling have been reported as possible methods to increase drug penetration.

Many studies have been published about photodynamic therapy (PDT) associated with an ablative method for nonmelanoma skin cancer (Zhang et al. 2011), extra Paget's disease, and porokeratosis treatment (Fukui et al. 2009). More recently, newer studies report this technique in cosmetic dermatology as an option in the treatment of stretch marks and hypertrophic scars (Issa et al. 2012, 2013).

Procedure and Mechanism of Action

TED through classic ablation methods is based on applying a fractional ablative laser or a fractional ablative radiofrequency (RF) device. The fractional ablation produces micro-perforations in the epidermis, allowing the permeation of drugs topically applied into the skin through these channels (Fig. 1).

TED with nonablative lasers is very recent approach with the aim of enhancing the drug penetration without significantly compromising the skin barrier function. It is postulated that nonablative laser promotes the loosening of intercellular adherence facilitating the penetration of substances.

In both methods, with ablative and nonablative lasers, the drug should be applied just after the laser.

The microneedling technique (MT) is also used as a way to trespass the stratum corneum to deliver active ingredients to the skin in a more efficient way. The MT uses micron-sized needles that can perforate the skin in a minimally invasive and low pain level manner, thereby creating aqueous transport pathways within the skin referred to

as microchannels (Milewski et al. 2010; Henry et al. 1998; Noh et al. 2010). It is not known although if after the microneedling blood and fibrin will invade the microchannels creating a new barrier for this penetration. Therefore, for MT it is recommended to do an inverse technique where the drug is applied prior to the MT and prior to each pass to guarantee more efficient delivery of the active ingredient.

Drugs for TED

Many substances, cosmeceuticals or medicaments, can be used for TED purpose and are chosen according to the disease to be treated (Sklar et al. 2014).

When associating TED with PDT, methyl aminolevulinate (MAL) is applied after laser or microneedle treatment. For hypertrophic scars (Issa et al. 2012) and areata alopecia (Issa et al. 2015), triamcinolone is indicated. Retinoic acid and vitamin C are indicated for stretch marks (Issa et al. 2013).

Possible drugs to be assisted by lasers for rejuvenation include tretinoin 0.05% cream, vitamin C 5–10% (cream or serum) alone or combined with other components such as ferulic acid (Waibel and Wulkan 2013), and hyaluronic acid 5%. Hydroquinone 4% associated or not with glycolic acid 10% cream, kojic acid 2%, phytic acid 2%, and tranexamic acid 5% cream can be used for melasma.

For all indications cream, serum, and solutions are the best vehicle, as gel formulations may dry very fast (Table 1). Sterilized substances are ideal choice for this purpose, but some topical cosmeceuticals have been used without complications.

Table 1 Dermatosis indications and possible drugs to be used for TED

Clinical indication	Possible drugs
Photodamaged Skin	Retinoic acid (0.025–0.005%) Hyaluronic acid 0.1–1% Vitamin C 5–10%
Melasma	Hydroquinone 4% Phytic and kojic acid 2% Tranexamic acid 5%
Acne scars	Retinoic acid (0.025–0.005%)
Scars	Retinoic acid (0.025–0.005%) Hyaluronic acid 0.1–1% Vitamin C 5–10% triamcinolone acetonide 10 mg/ml
Stretch marks	Retinoic acid (0.025–0.005%) Hyaluronic acid 0.1–1% Vitamin C 5–10%
Areata alopecia	Triamcinolone acetonide 10 mg/ml
Hypertrophic scar	Triamcinolone acetonide 10–40 mg/ml
Actinic keratosis (TFD)	ALA, MAL

TED with Ablative Lasers and Ablative Radiofrequency

In 2003 and later on, the initial studies about fractioned ablative lasers capable of producing ablation and TED were published, including Erbium:YAG and CO_2 lasers (Haerdersdal et al. 2010; Gómez et al. 2008; Stumpp et al. 2005; Wang et al. 2004; Lee et al. 2003; Baron et al. 2003).

At the same year Sintov et al. reported the use of radiofrequency in the formation of skin microchannels, communicating the stratum corneum with the deeper layers of the epidermis (Sintov et al. 2003). Later, other studies reported the microneedling technique with the same purpose (Donelly et al. 2008; Mikolajewska et al. 2010).

Lasers produce vaporization and coagulation, besides the thermal effect. This occurs in different proportions according to the wavelength used (Sklar et al. 2014). Ablative RF (electromagnetic waves) produces micro-sparks by oxygen ionization (micro-plasma) causing epidermal microchannels (Tachibana and Tachibana 1991).

In 2010, a low-frequency and high-pressure US, called impact US, was introduced in the market to increase drug penetration when associated with ablative methods. These US waves act by propelling molecules through preformed

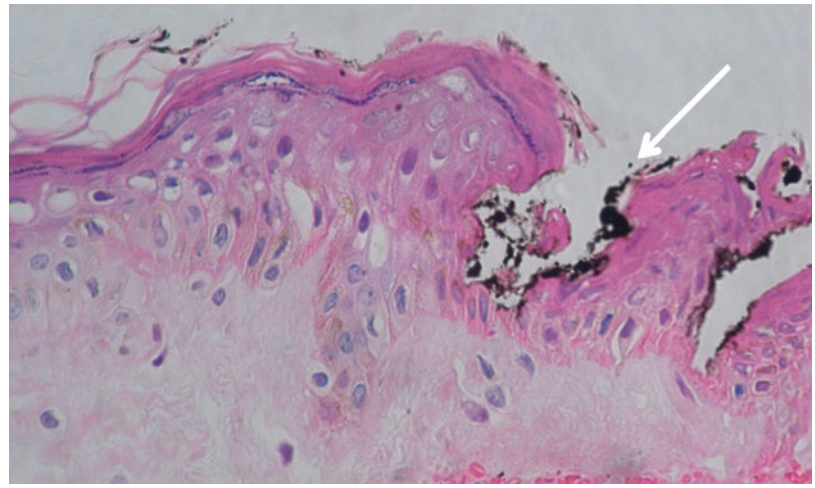

Fig. 2 Histopathological study (H&E stain ×400) of in vivo human skin: microchannels produced by ablative RF and black ink mainly locate inside the channels after applying acoustic pressure wave US

channels. It has a new proposal of action and depends on the previous use of an ablative method (see chapter Microneedle use for Transepidermal Drug Delivery on Stretch Marks). A histopathological study (not published) of in vivo human skin showed that a black ink, topically applied after ablative RF, was mainly located inside the microchannels after the US application (Fig. 2).

Histopathological studies (with hematoxylin and eosin stain) about ablative lasers for TED revealed the presence of vertical channels into the skin by vaporization of columns of tissue. Ablative fractional lasers create a grid of microscopic treatment zones (MTZ) (Skovbølling Haak et al. 2011). Each MTZ is composed of ablated channels, the microscopic ablation zones (MAZ), and a border of carbonization surrounded by coagulated tissue (microscopic thermal zone) (Sklar et al. 2014), result from thermal damage by the light source (Taudorf et al. 2014). This pattern breaks the skin barrier, enhancing penetration of drugs.

The ideal parameters needed to create the skin channels absolutely vary on the laser type and device model. It has been shown, although, that the best results in drug permeation consist of an ablation of low density. Haak et al. described the impact of laser treatment density (% of skin occupied by channels) and molecular weight (MW) for fractional CO_2 laser-assisted drug delivery. Ablative fractional treatment substantially increased intra- and transcutaneous delivery of polyethylene glycols (PEGs) in a MW that ranged from 240 to 4300 Da. Increasing laser density from 1% to 20% resulted in augmented intra- and transdermal delivery, but densities higher than 1% resulted in reduced delivery per channel. Mass spectrometry indicated that larger molecules have greater intracutaneous retention than transcutaneous penetration (Haak et al. 2012; Haedersdal et al. 2014).

Skovbølling et al. conduced a histopathological study on an ex vivo animal skin model with a fractioned CO_2 laser (Medart, Hvidore, Denmark), with the aim to establish a standard model to document the histological tissue damage profiles after ablative fractional laser treatment. It was shown that the studied laser produced a cone-shaped lesion with the base being the circular epidermal surface lesion and the apex pointing toward dermis, and a proposed mathematical formula was able to predict cone volume. It was also demonstrated that ablation depth increased in a linear relation with increased laser energies, dermal ablation width increased slightly with increasing energies, and thickness of coagulation zone reached a plateau at a certain energy level (Skovbølling Haak et al. 2011).

Taudorf et al. conduced an animal ex vivo study with a 2,940 nm laser with the aim of

establishing the impact of laser parameters, staked pulses, and the tissue effects. It was shown that low pulse energy and high repetition rate required many stacked pulses at the same spot to induce ablation, whereas high pulse energy delivered by decreased pulse repetition rate and fewer stacked pulses led to ablation by less applied total energy. Ablation depth was likewise affected not only by total energy delivered by pulse stacking but also by variations in pulse energy, pulse repetition rate, and pulse duration. Low pulse repetition rate (Hz) and reduced number of stacked pulses are important to avoid progressive accumulation of residual heat by allowing the exposed tissue to cool and ablation plume to be evacuated between pulses, otherwise leading to shallow wide craters instead of increasing ablation depth. It was also discussed that the advantage of using Erbium: YAG (2,940) laser instead of CO_2 laser is the possibility of creating purely ablated tissue with virtual no coagulation zone. Although the importance of the coagulation zone is not completely established, a thick coagulation zone may pose a significant induced barrier for molecule delivery (Taudorf et al. 2014).

Brauer et al. demonstrated that fractional treatment results in untreated areas between the MTZs allowing a more rapid healing response (Brauer et al. 2014).

Investigation of the optimal channel depth and channel density continues and will likely be dependent on each topical drug's chemical structure and the desired clinical target.

TED with Nonablative Lasers

TED performed with nonablative lasers is an innovative approach that rivals with the original concept of drug delivery. It is based on the thought that the damage caused by the light source temporarily looses the intercellular adherence by destroying lipids between cells. There are no proper tunnels as seen in ablative methods, but rather gaps between cells which drugs can travel through (Bloom 2014).

Different lasers can be used for this purpose such as Ruby and Erbium:Glass. As described with ablative sources of light, once the laser treatment is done, the topical formulation is applied (Lim et al. 2014; Lee et al. 2002).

Fig. 3 Devices for microneedling procedure: Dermaroller and Dermapen

The positive aspect of this approach is the shorter downtime, as the barrier function of the skin is quickly restored.

TED with Microneedle

The microneedle devices such as Dermaroller and Dermapen (Fig. 3) create microtunnels that vary from 0.5 to 2.5 mm. As with lasers the microneedling technique started being used as a way to trespass the stratum corneum to deliver active ingredients to the skin in a more efficient way. The stratum corneum, skin's outermost layer, is a barrier that prevents molecular transport across the skin (Menon et al. 2012). Therapeutic agents, such as peptides, proteins, and oligonucleotides, are difficult to deliver by conventional methods or topical delivery. The microneedling techniques are micron-sized needles that can perforate the skin in a minimally invasive and low pain level manner, thereby creating aqueous transport pathways within the skin referred to as microchannels (Milewski et al. 2010; Henry et al. 1998; Noh et al. 2010).

Moreover, these microchannels have no limitation regarding the size of molecules that can pass. In terms of size, the microchannels are in the range of microns, while the macromolecules delivered are typically nanometers in size (Kumar and Banga 2012; Petchsangsai et al. 2014). The question remains if after the microneedling blood and fibrin will invade the microchannels creating a new barrier for this penetration. Therefore it is recommended to do an inverse technique where the drug is applied prior to the microneedling technique and prior to each pass to guarantee more efficient delivery of the active ingredient.

Indications

Many different indications of TED have been reported. In most cases the studies were conducted with fractioned ablative lasers and some others with nonablative and with microneedling technique.

There are some reports of better clinical results with fractioned laser associated with PDT for actinic keratosis, superficial and nodular basal cell carcinomas, and Bowen disease (Zhang et al. 2011; Sklar et al. 2014). The efficacy of TED for genital warts, enhancement of topical anesthesia, vaccine immunization (Sklar et al. 2014), stretch marks (Issa et al. 2013), hypertrophic scars (Issa et al. 2012), areata alopecia (Issa et al. 2015), with both fractioned laser and ablative RF, have been reported. Other cosmetic indications include photoaging and melasma (Sklar et al. 2014).

Side Effects

Local side effects can be related to the lasers and to the drugs applied. They include redness, swelling, pain, crusting, transient residual hyperpigmentation, and infections. Systemic side effect can be related to the drugs applied and it is also a possibility.

Conclusions

Different methods can be used to produce microchannels in the epidermis with the aim to increase drug penetration, including RF, ablative and nonablative lasers, and microneedles. The laser's wavelength and the better parameters are not completely established; however it has been reported the importance of low density when using fractioned ablative lasers. The use of cosmeceuticals and drugs, usually topically applied, or injectable medications through TED can improve the therapeutic efficacy of these substances and can promote better results than laser or microneedles isolated.

TED can be considered a new effective method in dermatology, not only for diseases but also for cosmetic indications.

Take-Home Messages

- TED through ablation methods produces micro-perforations in the epidermis, allowing the permeation of drugs topically applied into the skin through these microchannels.

- TED with nonablative lasers is based on the thought that the damage caused by the light source temporarily looses the intercellular adherence by destroying lipids between cells.
- Microneedling technique is also used to deliver active ingredients to the skin, but it is questionable if blood and fibrin inside the microchannels formed through microneedling can create new barrier for this penetration.
- The ideal parameters needed to create the skin channels will absolutely vary on the laser type and device model. It has been shown, although, that the best results in drug permeation consist of an ablation of low density.
- Many substances, cosmeceuticals or medicaments, can be used for TED purpose and are chosen according to the disease to be treated.

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Photodynamic Therapy

Maria Claudia Almeida Issa and Diego Cerqueira Alexandre

Abstract

Photodynamic therapy (PDT) consists of a chemical reaction activated by light source that is used in the management of many skin diseases. The most extensively studied photosensitizing agents for PDT are 5-aminolevulinic and methyl aminolevulinate (MAL). The light sources used in photodynamic therapy should emit light at optimal wavelengths to excite the photosensitizer and produce reactive oxygen species. PDT should be considered as a therapeutic option, particularly in the case of non-melanoma skin cancer such as actinic keratosis, basal cell carcinoma, and Bowen disease. It can also be used in some inflammatory and infectious disease. Photorejuvenation is a new spectrum of PDT use, which is being widely studied. Daylight-mediated PDT is a new modality of PDT, which was developed to minimize patient discomfort, maintaining PDT efficacy. This chapter will approach its concept, mechanism of action, procedure, and indications.

Keywords

Photodynamic therapy • Non-melanoma skin cancer • Photosensitizer • Light source • Skin rejuvenation • Acne • Daylight-mediated photodynamic therapy

Contents

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Introduction

Photodynamic therapy (PDT) is a relatively novel procedure in the management of skin disease, mainly non-melanoma skin cancer (NMSC). It consists in the interaction between a topical or systemic photosensitizer, the appropriate activating wavelength of light, and oxygen, resulting in the formation of reactive oxygen species (ROS) in damage tissue. Those ROS affect all intracellular components, resulting in cell death.

Differently from other dermatological procedures, the association of PDT with topical photosensitizer has the capability of minimizing surrounding tissue damage, which gives an outstanding cosmetic result. PDT is able to selectively and effectively target and simultaneously treat lesions over large surface areas with little or no risk of scarring. Although there are many studies in the literature proving the efficacy of PDT in the treatment of actinic keratosis (AK) and NMSC, this procedure has others applications, including skin rejuvenation.

Nowadays, a new modality of PDT, called daylight photodynamic therapy (DLPDT), which uses sunlight instead of artificial light, is approved for actinic keratosis treatment with the same efficacy and reduced side effects compared to conventional PDT (Ozog et al. 2016; Osiecka et al. 2012; Christensen et al. 2010; Torezan et al. 2009).

History

The knowledge of the power of the combination between light and substances is antique. Ancient civilizations have known for thousands of years that they could combine different species of plant with sunlight to treat an enormous variety of skin diseases. However, it was only in the twentieth century that PDT was created by Hermann von Tappeiner, in Munich. He not only described an oxygen-dependent reaction following photosensitization but also developed the concept of PDT and described the first cases in human being. Since then, many photosensitizers have been used.

In 1990, Kennedy first reported the use of 5-aminolevulinc acid (ALA) as a topical photosensitizer for PDT on skin conditions. ALA was revolutionary because the use of topical photosensitizer to treat skin disease could avoid systemic side effects. At the end of 1990s, methyl aminolevulinate (MAL), an esterified form of ALA, was developed. Both substances have the same mechanism of action, but MAL has lipophilic properties, which gives increased penetration through cell membranes. Furthermore it has tumoral specificity, minimally affecting the surrounding tissue (Ozog et al. 2016; Osiecka et al. 2012; Christensen et al. 2010; Torezan et al. 2009).

Concept and Mechanism of Action

Topical photodynamic therapy relies on three basic principles: topical photosensitizer, light, and oxygen. The combination of them generates ROS that induce cell death, but minimally affect the surrounding tissue. At the beginning, only systemic photosensitizers were available to be used in PDT. Nevertheless, the advent of topical application revolutionized this procedure. ALA and MAL are the principal prodrugs used for PDT. They are exogenously applied on the lesion and are selectively absorbed and stored by hyperproliferative cells, such as tumoral cells, partly because of the altered enzyme activity in hemosynthesis.

ALA is the first compound synthesized in the porphyrin–heme pathway inside the mitochondria by ALA synthase, which is a rate-limiting enzyme and is converted endogenously into porphyrins, mainly protoporphyrin IX (PpIX) – a potent photosensitizer. Exogenous ALA is a hydrophilic agent and has a low molecular weight that allows it to easily penetrate the stratum corneum and bypasses the rate-limiting enzyme, overwhelming the cell of PpIX. Maximum concentration of photosensitizer PpIX has been shown to occur about 6 h after the end of 4-h incubation of ALA 20%

and is cleared from the skin within 24–50 h after the application. An alternative to ALA is the methyl ester form (MAL). The presence of methyl ester group makes the molecule more lipophilic and enhances penetration. Although MAL must be demethylated back to ALA by intracellular enzymes, it reaches maximal intracellular concentrations of PpIX quickly, allowing a shorter incubation period.

Here upon, the damage area is exposed to an appropriate wavelength of light, activating PpIX, which starts a photodynamic reaction in the presence of oxygen. Several light sources, including coherent and incoherent light, have been used in PDT. Blue light, which includes the wavelength of 405 nm, efficiently excites PpIX and is commonly used. Its penetrates about 2 mm, because of its relatively short wavelength, whereas red light (635 nm) is used for thicker lesions due to its greater capacity of penetration (>2 mm). Red light does not excite PpIX as efficiently as blue light; hence a higher fluence (dose) and a longer irradiation period are needed. However, many red light devices in use have a higher fluence compared with blue light devices and thus the time to treat can be quite similar. It is important to consider the fluence (J/cm^2) and irradiance (mW/cm^2) that are used in PDT. The effective photobleaching dose for a light source of approximately 405 nm is 10 J/cm^2, and a tenfold increase, or 100 J/cm^2 for a light source of 635 nm. In addition, because PDT consumes oxygen, it is important to use an appropriate rate of fluence as a high irradiance may consume the oxygen molecules too quickly, leading to a decrease in efficiency. Light-emitting diode (blue or red light) is commonly used for topical PDT. Red light is the best choice for carcinoma treatment, as it penetrates deeper.

As light source, lasers provide precise doses of light radiation. Lasers used in PDT include the tunable argon dye laser (blue–green light, 450–530 nm), the copper vapor laser-pumped dye laser (510–578 nm), long-pulse pulsed dye lasers (585–595 nm), the Nd:YAG KTP dye laser (532 nm), the gold vapor laser (628 nm), and solid-state diode lasers (630 nm). Fractionated ablative lasers are increasingly used to pretreat lesions, enhancing penetration and efficacy across multiple indications.

The reaction produces ROS, especially cytotoxic singlet oxygen. The ROS affect all intracellular components, including proteins and DNA, resulting in necrosis or apoptosis of the tumoral cells without affecting the peripheral normal ones. Due to its selectivity of tumor tissues, ALA/MAL-PDT procedure has the advantages of high efficacy, low downtime procedure, no scar formation, no cumulative effects, no drug resistance, and being effective for recurrent patients (Ozog et al. 2016; Osiecka et al. 2012; Christensen et al. 2010; Torezan et al. 2009; Neves et al. 2016; Pauwels et al. 2011; Foley 2005; Wang et al. 2016; Wlodeck et al. 2012; Lv et al. 2016).

Indications: Approved and Off-Label

PDT associated with topical ALA/MAL is mainly indicated for treating precancerous lesions, such as AK, as well as Bowen's disease (BD) and basal cell carcinoma BCC (except morpheaform and pigmented BCC). PDT is particularly suitable for treatment of multiple or extensive skin lesions; areas with multiple and recurring precancerous and cancerous lesions (field cancerization); areas where the cosmetic outcome is very important, such as the face, neck, and hands; or areas where it is difficult to achieve a good cosmetic result with the use of other dermatological procedures. PDT is not recommended in pregnancy, breastfeeding, or in patients with porphyria, and it is not effective in morpheaform BCC and pigmented lesions.

For recurrent, pigmented, indurated, eroded, or ulcerated keratotic tumors, biopsies for histological examination should be performed before PDT indication. Biopsies of thicker lesions are also indicated in multiple keratotic lesions in an area with field cancerization and in patients with immunosuppression (Osiecka et al. 2012; Christensen et al. 2010; Foley 2005; Gong et al. 2016).

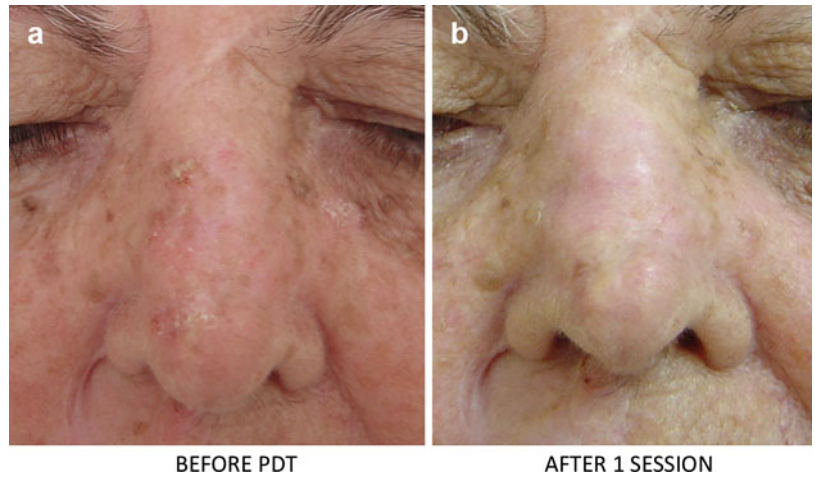

Fig. 1 Actinic keratosis lesions on the nose before and after one session of MAL-PDT with red light

Actinic Keratosis

Actinic keratosis, also known as solar keratosis, is the most common premalignant dermatological pathology, caused by accumulation of genotoxic DNA damage, generated by ultraviolet (UV) light exposure, particularly UVB. Its incidence is increasing due to progressive aging of the population and the higher cumulative lifetime exposure to UV light. Treatment of AK lesions is motivated by both their propensity to progress to squamous cell carcinoma and cosmetic considerations. Nowadays, several treatment options are available, and the therapeutic decision is based on the assessment of the clinical features, among which the number and thickness of the lesions and the clinical aspect of the surrounding skin have a prominent importance. PDT associated with topical photosensitizer MAL is a highly effective first-line treatment (one session) with an average of complete response rates of up to 90% and an excellent cosmetic outcome (Fig. 1) (Ozog et al. 2016; Wlodeck et al. 2012; Gong et al. 2016; Braathen et al. 2008; Zane et al. 2016).

Bowen's Disease

Bowen's disease (BD) is SCC in situ, characterized as full-thickness epidermal atypia without invasion into the dermal layer. Multiple studies have demonstrated the effectiveness of PDT in treating BD (two sessions 1 week apart), with a clearance rate of 80–82% in clinical practice (Fig. 2). PDT has demonstrated promising results in the treatment of BD, whereas for invasive SCC it has not revealed positive outcomes. Therefore, invasive SCC is not indicated for PDT (Ozog et al. 2016; Pauwels et al. 2011; Wlodeck et al. 2012; Gong et al. 2016; Morton 2005).

Basal Cell Carcinoma

Basal cell carcinoma is the most frequent type of skin cancer and arises from the basal cells of the epidermis. They are mainly located in sun-exposed areas like the face, the neck region, extremities, and the trunk and then rarely metastasize. There are three major grouped variants of BCC: superficial, nodular/micronodular, and morpheaform/sclerosing/infiltrative. Superficial BCC is defined by superficial basaloid cell buds. Aggregated basaloid cells that invade the dermis define nodular BCC and smaller clusters determine micronodular BCC. In morpheaform BCC, cords of basaloid cells extend between collagen bundles. Treatment of BCCs should be chosen according to clinical type, tumor size, and location. PDT (two session with 1 week apart) is commonly used to treat small uncomplicated superficial BCCs and thin (less than 2 mm depth) nodular BCC (Fig. 3). The use of PDT to

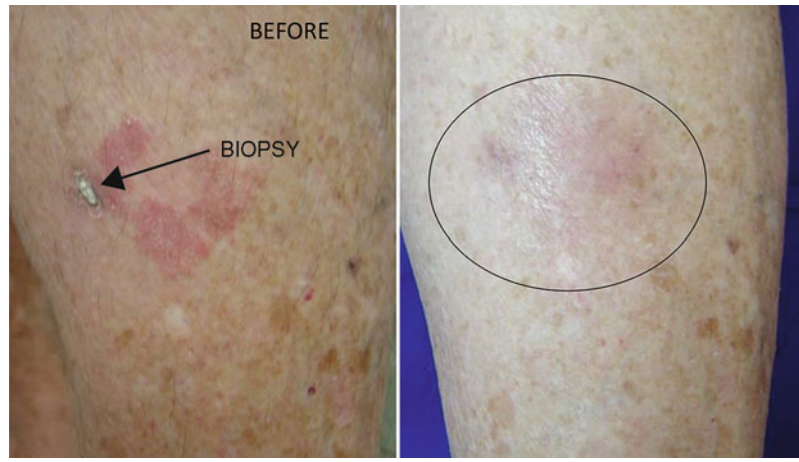

Fig. 2 Bowen's disease on the legs: before and 10 months after two sessions of MAL-PDT with red light

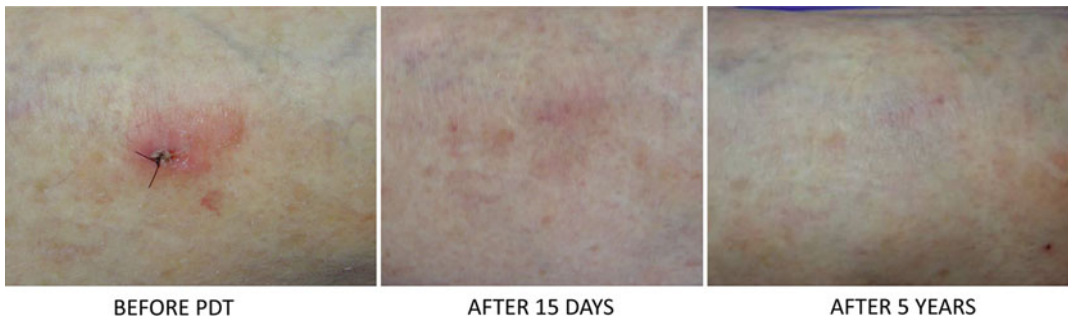

Fig. 3 Superficial BCC on the legs: before and 5 years after two sessions of MAL-PDT with red light

assist tumor reduction before surgery is discussed. PDT has the potential of becoming a first-line therapy in the treatment of patients with multiple lesions (e.g., Gorlin-Goltz syndrome or in immunosuppressed patients after organ transplantation), avoiding repeated surgical excisions and patients who do not have clinical conditions to undergo surgery.

Tumor thickness is a determinant response parameter of BCCs to PDT with MAL in combination with red light. Due to the limited penetration of this wavelength of light into tissue, tumor thickness should not exceed 2–3 mm to achieve complete response. Moreover, pigmented BCC should not be treated with PDT, because the pigments do not allow an optimal penetration of the light (Ozog et al. 2016; Osiecka et al. 2012; Neves et al. 2016; Pauwels et al. 2011; Gong et al. 2016; Szeimeis 2007).

Acne Vulgaris

Acne vulgaris (or simply acne) is a skin condition that affects people of all races and all ages, due to an inflammation of pilosebaceous unit. Acne lesions appear primarily on areas with high concentration of sebaceous glands such as the face, back, and chest. Sebaceous glands secret sebum, which consists of fatty acids that support the colonization by *Propionibacterium acnes*. PDT is among one of the extensively studied treatments that has demonstrated to be safe and effective in treating inflammatory lesions of acne vulgaris (Fig. 4). Nevertheless, it was seen that acne complete clearing was variable among patients and relapse rates were high after therapy discontinuation. Noninflammatory lesions do not seem to be affected. The different severity of acne lesions at different body sites has shown good response to

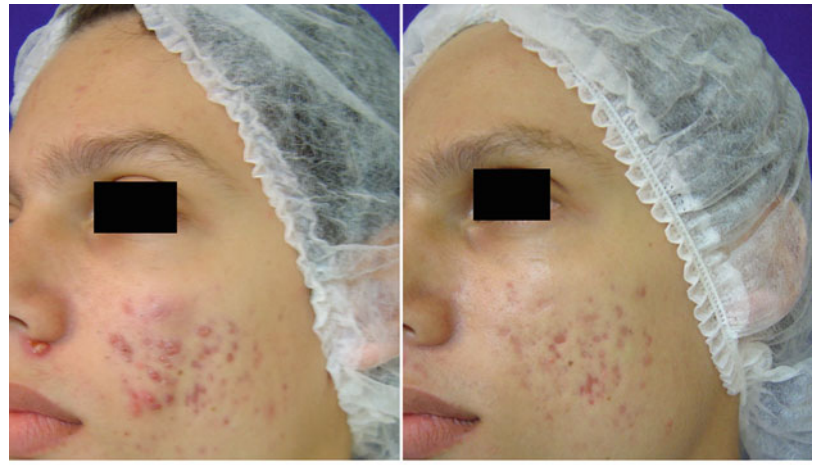

Fig. 4 Inflammatory acne lesions on the face before and 6 months after three sessions of MAL-PDT with red light

PDT and all skin types are eligible for PDT. This procedure is also a good option in those patients who are poor candidates for isotretinoin. Usually, three–six sessions are necessary (Ozog et al. 2016; Keyal et al. 2016).

Mycosis Fungoides

Mycosis fungoides (MF), also known as Alibert-Bazin syndrome or granuloma fungoides, is the most common cutaneous primary lymphoma. MF is classically classified according to its clinical presentation in spots, plaques, or tumors, usually on areas of nonexposed skin, although there are a wide variety of forms of presentation. PDT is a well-tolerated alternative with good cosmetic outcome for the treatment of localized MF plaques, especially those that do not respond to usual treatments. Also, it is a good option in difficult areas of treatment, such as the face, and areas at risk of poor healing. PDT is not a suitable treatment for tumor lesions and large or very numerous plaques. PDT obtains clinical improvement of MF plaques, but does not cure them, and thus it is necessary to periodically follow up the patients (Torezan et al. 2009; Fernández-Guarino and Jaén-Olasolo 2013).

Paget's Disease

Paget's disease is a rare neoplasm of the skin, which commonly occurs on mammary region of elderly women. Extramammary Paget's disease (EMPD) mainly targets genital skins and its exact incidence is unknown, but it is estimated to account for 1–6% of all cases of Paget's disease. The lesions are typically erythematous or leukoplakic plaques. Symptoms such as pruritus, pain, and a burning sensation are common. MAL-PDT has demonstrated efficacy in treating NMSC and has also been used with some success to treat Paget's disease and EMPD. As this treatment is not curative, the most interesting outcome is the promising control of the symptoms that is achieved in a vast majority of the patients. MAL-PDT is able to control large and multiple lesions regardless of the area involved, preserving cosmetic and/or functional anatomy (Fontanelli et al. 2013).

Conventional PDT Treatment

Treatment Procedure

- Registration of lesions: the localization of the lesions should be registered on a separate form or photographed. The extent of the lesion must be noted onto the form.
- Anesthesia: some studies have shown that the application of topical anesthetics before phototherapy must not be performed, because the acid pH of the anesthetics may inactivate the photosensitizer. Local anesthesia without

epinephrine, as vasoconstriction should be avoided, can sometimes be used during light exposure. Usually, anesthesia is not used.

- Preparation includes abrasion, curettage, debulking, and tape stripping:
  - Abrasion: removes only hyperkeratoses, crusts, and the stratum corneum, to improve the uptake of MAL cream into the skin.
  - Curettage: removes hard keratotic tissue. As tumors may have subclinical extensions, to minimize the possibility of recurrences, it is recommended to scrape 5 mm of the surrounding tissue of normal appearance.
  - Debulking: is used to reduce the thickness of the tumor. The cosmetic outcome is considered favorable.
  - Tape stripping: can be used as a supplement to curettage in the treatment of AK on the lips and in the preparation of large skin areas. Studies recommend to use tape with strong adhesive properties. The tape is applied onto the treatment area and then pulled off sharply, thus removing the upper part of the epidermis.
- Treatment of bleeding: bleeding should be stopped before the application of topical photosensitizer.
  - Compression with a normal compress (gauze)
  - Elevation of the bleeding area if possible.
- Application and removal of cream: MAL is applied as a 1-mm-thick layer on the prepared skin area and on the lesion and 10 mm around. MAL's incubation time before illumination is 3 h when treating NMSC; short period can be used for skin rejuvenation. ALA's incubation time was first described as 14–18 h, but many studies had reported 3 h, similar to MAL. The photosensitizer should be occluded with a curative (plastic film + occlusive bandage) during incubation time. Before exposure to light, photosensitizer is removed using a small compress with or without saline solution. There is no need for further washing or cleaning of the treatment area.
- Drug delivery: the use of microneedling rollers or fractional ablative lasers has been studied and shown to promote better photosensitizer penetration, absorption, and activation (Ozog et al. 2016; Christensen et al. 2010; Torezan et al. 2009).

Light Sources

Broadband and narrowband light or lasers may be used for topical PDT. Light treatment starts immediately after removal of the bandage. The distance between the LED lamp and the skin is usually 5–8 cm. For MAL-PDT, prime experience is gained by using red light (635 nm), not heat producing, from light-emitting diodes (LEDs) with a light dose of 37 J/cm^2 and the exposure time 7–9 min. For 5-ALA, blue light (417 nm) has to be used with a total dose of 10 J/cm^2. Both the patient and the physician should protect their eyes with special glasses. Prolonged exposure to blue and ultraviolet light is damaging to the retina and increases the risk of cataracts. All staff or providers should wear appropriate eyewear before entering the room. The room should also have adequate cooling and ventilation for the light source (Ozog et al. 2016; Christensen et al. 2010; Torezan et al. 2009).

Treatment of Actinic Keratosis

Thin or moderately thick AK is treated just once. If after 3 months, the treatment effect is insufficient, and a repeat treatment is given, with a later 3-month follow-up. These lesions do not need further treatment if clinically cleared at the 3rd month follow-up. Hyperkeratotic AK, AK with histopathological severe atypia, and AK in patients with immunosuppression are treated twice with 1 week apart and they should be followed up for 12 months.

For the treatment of actinic damage (photorejuvenation) on the face, incubation times of 1–2 h are commonly used in clinical practice, but usually better results are achieved with two–three sessions with 4 weeks apart (Fig. 5) (Ozog et al. 2016; Christensen et al. 2010; Torezan et al. 2009).

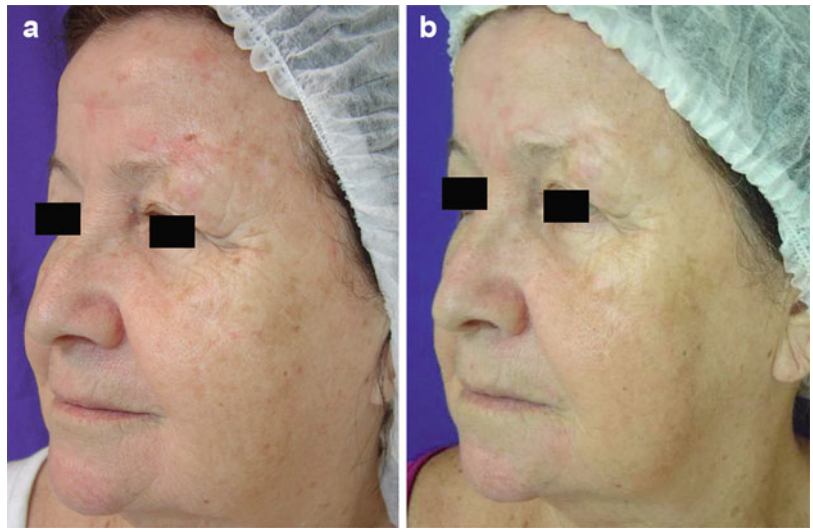

Fig. 5 Field of cancerization on the face before and 6 months after two sessions of MAL-PDT with red light

Treatment of Bowen's Disease

BD is treated twice with 1 week apart and followed up for at least 12 months. A prolonged follow-up is required if the patient has genital localization (Christensen et al. 2010; Torezan et al. 2009).

Treatment of Basal Cell Carcinoma

Basal cell carcinoma has the same treatment time as BD. It is treated twice with 1 week. Primary, small superficial BCC is followed up for at least 12 months. Other BCCs have to be followed up once a year for at least 5 years (Christensen et al. 2010; Torezan et al. 2009).

Adverse Effects

The most common adverse effects are localized phototoxic reactions in the treatment area and, during illumination, several degree of pain. Systemic adverse effects such as nausea, fatigue, paresthesia, and headache are very rare. Erythema and edema are frequently experienced reactions at the treatment site, as are warm skin, scaling, itching, and transitory postinflammatory hyperpigmentation.

As PDT is known to induce inflammation in the treated area, pigmentation changes are expected. Both hyperpigmentation and hypopigmentation have been reported with both MAL and ALA, with a higher incidence with ALA. This risk may be greater in patients with skin types IV–VI. As in other cases with postinflammatory pigmentation, this usually resolves with time. Still less frequent reactions are urticaria, infection, and contact dermatitis. The treatment of these conditions should be done with potent topical steroids. High-sun (mineral-based or physical sunblocks) protection factor is used for at least 6 weeks to avoid or limit postinflammatory hyperpigmentation. Covering with opaque clothing is the best way to avoid additional photoreactivity, as is using a wide-brim hat if stepping outside immediately after treatment and during the postoperative period.

Some patients experience very short-lasting pain during photosensitizer application. During exposure to light, all patients will experience some degree of pain. Stinging, burning, pricking, and itching are also described by patients. The degree of pain may be experienced differently at various treatment sessions. The mechanism of action of pain in PDT is not yet clarified, but it is thought to be secondary to the interaction between the inflammation caused by cell death and myelinated A delta or unmyelinated C fibers. Multiple factors play an important role in the amount of pain

experienced. These factors include the type of photosensitizer used, location of lesions, extent and type of lesion, amount and rate of energy delivered, type of light source, number of sessions, and skin phototypes. MAL-PDT gives less pain than ALA-PDT. This may be explained by the fact that MAL is more selectively absorbed by abnormal cells when compared with ALA. The pain usually occurs during light exposure and may last for some hours and usually disappears on the same day.

Several strategies have been studied found to be helpful in reducing the level of pain, but not completely eliminating it. These include cold air, injectable anesthetics, reducing irradiance (including daylight-mediated PDT), and interrupting the PDT session (Ozog et al. 2016; Christensen et al. 2010; Neves et al. 2016; Chaves et al. 2012; Sunar et al. 2013).

PDT: New Modality with Daylight

A new modality of photodynamic therapy was developed to minimize patient discomfort during conventional PDT and reduce patient and staff time spent performing PDT. Daylight PDT involves the use of a photosensitizer, MAL, and a natural source of light, the sunlight. The spectrum of visible light of the sun (red and blue light) is used to activate the photosensitizer. To start the procedure, it is necessary to apply chemical (organic) sunscreens on patient's skin, protecting against UV radiation. Physical (inorganic) sunscreens cannot be used, as they are able to block visible light. After 15 min, a gentle curettage of the AK lesions should be done before applying MAL, which is not occluded as in conventional PDT. After MAL application, and in 30 min, patient should undergo daylight exposure for 2 h. The mechanism that explains the reduction of patient discomfort during the procedure is the limitation of the buildup of PpIX before and during PDT. This was accomplished because the daylight-mediated PDT protocol uses a short incubation period of 30 min before PpIX activation by daylight exposure-coupled constant activation of PpIX during daylight exposure.

Additional benefits of the procedure include minimal patient time spent in the clinic, minimal staff time supervising the procedure and no requirement for the purchase of a light source. Daylight-mediated PDT should not be performed in cloudy or rainy days. It is approved for AK lesions and field of cancerization, but not to carcinomas (Ozog et al. 2016; Wiegell et al. 2012).

PDT X Cosmetic Procedures

UVA and UVB radiation are responsible for photoaging, which is characterized by loss of skin elasticity, roughness, deep wrinkles, and pigmentations, mainly due to degradation of collagen. Direct ultraviolet (UV) light absorption and ROS-mediated photochemical reactions mediate photoaging. Metalloproteinases (MMPs) induced by ultraviolet (UV) radiation damage the dermis and degrade collagenous and noncollagenous proteins from the skin extracellular matrix.

Because the amount of collagen in the skin decreases with age, it becomes more challenging to rejuvenate photoaged skin in elderly people. In the last decade, lasers and therapies based on non-laser light, such as IPL, LED, and PDT, have become popular in dermatology. There is enough clinical evidence to demonstrate improvement in aging skin with the use of PDT. This procedure is a new option to treat photodamaged skin and can be performed in any skin type.

PDT may induce an inflammatory response in the photodamaged skin, with subsequent dermal remodeling. MAL-PDT could induce MMP-9 to degrade the fragmented elastic fibers and degenerated collagen in small fragments of proteins, leading to synthesis of new collagen. Therefore, MAL-PDT could induce new collagen formation, mainly after 3 months from treatment, to enable repair of the damage. Effects of PDT are not limited to the site where photosensitization takes place, but are spread in a chain reaction. Usually, two–three sessions 4 weeks apart are necessary. Clinically, improvement in skin texture, wrinkles, and pigmentation is observed (Osiecka et al. 2012; Torezan et al. 2009; Issa et al. 2009, 2010). DLPDT for skin rejuvenation

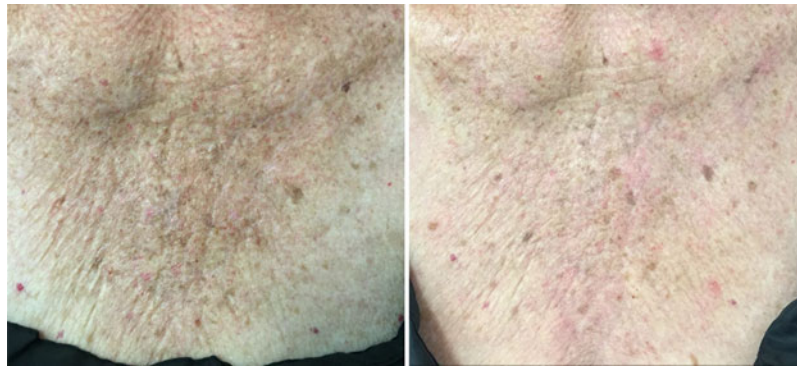

Fig. 6 Field of cancerization on the trunk before and 3 months after MAL-DLPDT pretreated with CO_2 laser. Reprinted from Issa et al. Surg Cosmet Dermatol 2016;8(4 Suppl. 1):S23–33

is a very new option and some initial cases showed promising results (Fig. 6).

Conclusion

Photodynamic therapy associated with topical photosensitizer is an effective dermatological procedure. PDT is very well-established treatment for AK and for NMSC. Many studies reported good efficacy of PDT for cosmetic procedures (photorejuvenation and acne vulgaris treatment). PDT has the capability of reducing surrounding tissue damage, which gives an outstanding cosmetic result. Furthermore it is a very practical procedure for dermatologist, with low downtime for the patient. These properties differentiate PDT from other dermatological procedures.

A new modality of PDT, called daylight-mediated PDT, is now approved for AK treatment maintaining conventional PDT efficacy, but reducing patient's discomfort during the procedure. Some initial cases using DLPDT for skin rejuvenation associated with laser or microneedling pretreatment showed promising results.

Take-Home Messages

- Photodynamic therapy is an effective treatment modality in dermatology. It is approved for AK and NMSC lesions, but many reports show its efficacy for nonneoplastic disease.
- PDT is a relative new option of photorejuvenation, improving photodamaged skin in any skin type. Acne is also described as a PDT indication in cosmetic dermatology.
- Photodynamic therapy relies on three basic principles: topical photosensitizer, light source, and oxygen.
- The management of pain associated with PDT is of great importance to ensure patient comfort.
- Daylight-mediated PDT is a new modality of PDT approved for AK treatment and is widely used due to its efficacy and practicality. Some initial cases of photodamaged skin treated with DLPDT showed good results for photorejuvenation.

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Botulinum Toxins

Ada Regina Trindade de Almeida and Yanna Kelly Silva

Abstract

Botulinum toxin (BoNT) has been used over the last 40 years in different medical specialties. Since then its use has been expanded over the decades to new indications, particularly in dermatology. It produces chemodenervation of muscles by inhibiting acetylcholine release on the neuromuscular junction and has been used in cosmetics to treat hyperfunctional and hyperdynamic lines and wrinkles of the face and neck as well as localized hyperhidrosis. It is currently recognized as a safe and effective treatment when standard techniques and recommended doses are used. Due to its mechanism of action, therapeutic doses are extremely small, the effect is highly precise, and systemic adverse effects are rare. There are five sources of botulinum toxin A (BoNT-A) worldwide, but BoNT formulations are not identical or interchangeable.

Keywords

Botulinum toxin • Botulinum toxin A • Facial and neck rejuvenation • Cosmetic dermatology • Hyperhidrosis • OnabotulinumtoxinA • AbobotulinumtoxinA • IncobotulinumtoxinA • Botulinum toxin A Prosigne • Botulinum toxin A Neuronox • RimabotulinumtoxinB • Wrinkles • Glabellar region • Periorbital region • Crow's feet • Frontal region • Perioral region • Mental region • Marionette lines • Platysma

Contents

Introduction

Botulinum toxin (BoNT) has been used over the last 40 years in different medical specialties. The first clinical use was described during the late 1970s in ophthalmology to treat strabismus (Scott 1980). During that time cosmetic results in the periorbital area were also observed, and since then its use has been expanded over the last decades to new indications, particularly in dermatology (Carruthers and Carruthers 2008).

It is being increasingly used as an effective treatment of numerous diseases characterized by

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excessive or inappropriate muscle contraction such as strabismus, hemifacial spasm, blepharospasm, cervical dystonia, spasmodic dysphonia, spasticity, sphincters hyperfunction (vesical, anal, and esophageal), facial and neck rejuvenation, as well as autonomic disorders: hyperhidrosis, hypersalivation, and crocodile tears. In addition, BoNT use has been reported in the management of pain control with successful results in migraine/tension headache and myofascial pain. In Raynaud's phenomenon, besides pain reduction, it also improves the associated swelling and discoloration (Carruthers and Carruthers 2008; Carruthers et al. 2004).

The accumulated experience using BoNTs over the last years led to a better understanding of the muscular role in aging. BoNT is currently recognized as a safe and effective product, and it is expected to be widely used with new perspectives and indications being reported all the time, mainly in cosmetic area (Carruthers and Carruthers 2008; Carruthers et al. 2004; Sattler 2010).

Botulinum Toxin in Cosmetic Dermatology

Basic Concepts and Mechanisms of Action

BoNT is obtained from *Clostridium botulinum*, a Gram-positive anaerobic bacterium that produces seven types of neurotoxins (A, B, C1, D, E, F, and G) that are antigenically different but with similar molecular weights. Only two of them are commercially available: serotypes A (BoNT-A), which appears to be the most potent subtype, and B (BoNT-B). All of them produce chemodenervation by inhibiting acetylcholine release on the neuromuscular junction (Aoki 2005).

During the normal neurotransmission, the acetylcholine vesicle attaches to and forms a complex with three SNARE proteins: vesicle-associated membrane protein (VAMP or synaptobrevin), 25 kDa synaptosomal-associated protein (SNAP-25), and syntaxin. Together they fuse to the presynaptic membrane and the neurotransmitter is released at the synaptic cleft (Aoki 2005; Poulain et al. 2008; Arnon et al. 2001). BoNTs are also able of inhibiting the release of other neurotransmitters, such as substance P, noradrenaline, calcitonin gene-related peptide, glutamate, adrenaline, etc., from a variety of synaptosomal and neuronal systems (Poulain et al. 2008).

BoNT-A was the first neurotoxin to be developed for clinical use. It is naturally produced as a complex of a core neurotoxin protein, along with several hemagglutinin and nontoxic nonhemagglutinin proteins. The associated proteins serve to stabilize and protect the neurotoxin molecule from degradation (Chen et al. 1998; Sharma and Singh 1998; Trindade De Almeida et al. 2011).

Under physiologic conditions, the core 150-kDa protein dissociates from the toxin complex, binds to synaptic vesicle protein using the heavy chain component, which is selective to cholinergic nerve endings, and enters the neuronal cell by internalization (Chen et al. 1998, 2007; Sharma and Singh 1998; Binz and Rummel 2009).

Once in the cytosolic surface membrane, BoNT-A binds to and cleaves the SNAP 25, and the release of acetylcholine is blocked. This specific mechanism of action enables a small quantity of toxin to produce a significant effect (Binz and Rummel 2009; Chen et al. 2007). Then therapeutic doses are extremely small, the effect is highly precise, and systemic adverse effects are rare (Trindade De Almeida et al. 2011).

For the other hand, BoNT-B is the other commercially available serotype. It was approved in the USA for treatment of cervical dystonia in 2000 and has a different intracellular site of action: the vesicle-associated membrane protein (VAMP). This product is not available worldwide but only in Europe and the USA (Arnon et al. 2001; Chen et al. 1998, 2007; Binz and Rummel 2009).

Available Products

BoNT formulations are not identical or interchangeable. They possess individual potencies, and attention is required to ensure proper use and

avoid errors. In 2009, FDA established drug names to reinforce these differences and prevent potential serious risks associated with these medications (Trindade De Almeida et al. 2011; Parrish 2003).

Currently, only one form of BoNT-B is available under the name of rimabotulinumtoxinB and trade name of Myobloc/NeuroBloc (Solstice Neurosciences Inc./Eisai Co., Ltd.) in the USA and NeuroBloc in Europe. The US FDA approved it for cervical dystonia in 2001 (http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm174949.htm (accessed in October 1st 2015; Myobloc 2009).

There are five sources of BoNT-A available worldwide (Table 1):

1. OnabotulinumtoxinA (OnaA): Botox/Botox® Cosmetic in the USA and Latin America (Allergan, Inc., Irvine, CA), also known as Vistabel® in Europe and Vistabex® in Italy (Botox 2010)
2. AbobotulinumtoxinA (AboA): Dysport® (Ipsen Ltd., Berkshire, UK) in the USA, Europe, and Latin America and Azzalure® in Europe (Dysport 2009)
3. Botulinum toxin A Prosigne® (Lanzhou, China) in Asia and Latin America (Prosigne 2005)
4. IncobotulinumtoxinA (IncoA): Xeomin® (Merz Pharma, Frankfurt) in Canada, Germany, the USA (for therapeutic use), and Latin America and Bocouture® in Europe and Latin America (Xeomin 2010)
5. Botulinum toxin A Neuronox®, Meditoxin®, and Botulift® (Medytox Inc., South Korea) (BTXA 2015)

Regarding the cosmetic use of BoNTs, OnaA is the one that possesses the highest amount of published information, followed by AboA and IncoA. Other BoNT-A formulations have sporadic data so far. Although not interchangeable, in daily practice, BoNT formulations conversion rate of 1U:1 U may be considered between OnaA and all 100-U product vials (IncoA, Prosigne, and NeuroBloc) and 1:2.5 U between OnaA and AboA (Trindade De Almeida et al. 2011; Parrish 2003).

Reconstitution, Storage, and Dilution

The standard reconstitution method for most BoNT-A's commercial products according to their package insert information is the addition of unpreserved saline. The manufacturers recommend that the vials should be stored before dilution at temperatures between 2 °C and 8 °C (OnaA and AboA) under refrigeration or between −5 °C and −20 °C (OnaA and Prosigne) in freezer. According to manufacturers, after being reconstituted, BONT-A should be used as soon as possible, within the interval of 4 h (OnaA) and 8 h (AboA), when kept at 2 °C and 8 °C. However these parameters are the subject of many published studies that reveals different forms of BoNT-A storage (Botox 2010; Dysport 2009; Prosigne 2005; Xeomin 2010; BTXA 2015).

Nevertheless, variations in these parameters are described in the literature including mixture with several substances, agitation and foam formation, and thawing and refreezing, revealing different ways of BoNT-A storage without losing efficacy. Some of these information are reviewed in this section.

Unpreserved Saline

The abobotulinumtoxinA recommended reconstitution method in a recent international consensus was to add unpreserved 0.9% sodium chloride to the lyophilized powder (Kane et al. 2010), while the suggested dilution to cosmetic purposes is 1–4 ml of saline to 100U.

Preserved Saline

Preserved saline (containing benzyl alcohol) when used as the reconstitution agent was proved as not affecting the potency of onabotulinumtoxinA and turning the injection less painful (in a bilateral, comparative, prospective study in 100 cosmetic patients) (Alam et al. 2002). Further two studies confirmed these observations: one comparative, double-blinded, side-by-side controlled trial with blepharospasm patients (Kwiat et al. 2004) and a single-blinded study with 93 individuals treated in the upper face, neck, and axillary regions (Sarifakioglu and

Table 1 Botulinum toxin manufacturer recommendations on supply, dilution, and storage

	OnabotulinumtoxinA	AbobotulinumtoxinA	BoNT-A	BoNT-A	IncobotulinumtoxinA	RimabotulinumtoxinA
Company	Allergan, Inc.	Ipsen, Inc./Medicis, Inc.	Lanzhou	Medytox Inc., South Korea	Merz Pharmaceuticals	Solstice Neurosciences Inc./ Eisai Co. Ltd.
Commercial names	Botox®, Botox Cosmetic®, Vistabel®, Vistabex®	Dysport®, Reloxin®, Azzalure®	Prosigne®, Lantox®, Redux®	Neuronox®, Meditoxin®, Botulift®	Xeomin®, Bocouture®	Myobloc®, NeuroBloc®
Approvals	Worldwide, including the USA and Canada	>65 countries, including USA and Canada	>10 countries, including China	Korea, India, Latin South America	Germany, other European countries, Mexico, Argentina, Brazil	the USA, some European countries
Type	Type A (Hall strain)	Type A (NCTC 2916 strain)	Type A	Type A	Type A (Hall strain)	Type B
Active substance	Botulinum toxin type A complex (900 kDa)	Botulinum toxin type A complex (400 kDa)	Botulinum toxin type A complex (900 kDa)	Botulinum toxin type A complex (940 kDa)	Botulinum toxin type A, free from complexing proteins (150 kDa)	Botulinum toxin type B (700 kDa)
Indications	Blepharospasm, cervical dystonia, glabellar lines, hyperhidrosis, chronic migraine	Blepharospasm, cervical dystonia, glabellar lines	Blepharospasm, cervical dystonia, glabellar lines, hyperhidrosis	Blepharospasm	Blepharospasm, cervical dystonia, cosmetic use in some countries	Cervical dystonia
Mode of action	SNAP 25/SV2	SNAP 25/SV2	SNAP 25	SNAP 25	SNAP 25	VAMP
U/vial	50, 100, or 200	300 or 500	50 or 100	100	50 or 100	2.500, 5.000, or 10.000
Pharmaceutical form	Powder dissolved in solution for injection	Powder dissolved in solution for injection	Powder dissolved in solution for injection	Powder dissolved in solution for injection	Powder dissolved in solution for injection	Solution
Excipients	500 µg HSA 0,9 mg NaCl	125 µg HSA 2,5 mg lactose	5 mg gelatin 25 mg dextran 25 mg sucrose	500 µg HSA 0,9 mg NaCl	1.000 µg HSA 4,7 mg sucrose	500 µ/mL HAS NaCl 0,1 M Dissodium succinate 0,01MHCl (to adjust pH) Water for injection
Storage before dilution	2–8 °C	2–8 °C	2–8 °C	2–8 °C	<25 °C	2–8 °C

Sarifakioglu 2005). Preserved saline was also chosen as the preferred diluent for reconstitution of onabotulinumtoxinA in a consensus panel held in 2004 (Carruthers et al. 2004). The possibility of benzyl alcohol activity as a local anesthetic was recognized by another expert panel, but this effect was considered negligible at low volumes (Kane et al. 2010).

Saline Plus Hyaluronidase

The viability of onabotulinumtoxinA as well as the possibility of enhanced diffusion with the addition of hyaluronidase to saline was tested by Goodman in 2003 (Goodman 2003). After 2 weeks, the initial results showed that the efficacy was not impaired, and greater diffusion of the effect was observed. Furthermore, no long-term results were evaluated.

Lidocaine and Epinephrine

Gassner and Sherris demonstrated in a double-blind, randomized, controlled trial with 10 volunteers for cosmetic indication that when 1% lidocaine with 1:100,000 epinephrine was used to reconstitute onabotulinumtoxinA, all components retained their function (Gassner and Sherris 2000). Similar results were found in two cases, reconstituting onabotulinumtoxinA with 2% lidocaine with 1:200,000 epinephrine (Haubner 2009).

Recently, the injection of a "cocktail" composed of abobotulinumtoxinA, 2% lidocaine with 1:100,000 epinephrine, and hyaluronic acid (Perlane, Medicis, Scottsdale, AZ) was described for rejuvenation of the upper face. Two syringes were connected to mix all products, and at least 10 back-and-forth mixings were performed. Five patients had the combined product injected into the periocular and glabellar areas in linear threads, small boluses, or serial punctures, and it was concluded that both efficacy and safety were not compromised (Kenner 2010).

In another study, 29 axillary hyperhidrosis patients were treated with onabotulinumtoxinA reconstituted in 2% lidocaine in one axilla and compared to normal saline in the other (Vadoud-Seyedi and Simonart 2007). The authors concluded that this treatment was equally effective in the short and long terms. Lidocaine-reconstituted onabotulinumtoxinA was associated with significantly less pain. For this reason, it might be preferable for treating axillary hyperhidrosis.

For the other hand, a fatal case of anaphylaxis after the injection of an onabotulinumtoxinA and lidocaine mixture in a woman for chronic neck and back pain was reported (Li et al. 2005). Although it was not possible to determine which substance was responsible for this reaction, it is advisable to consider that the use of lidocaine to dilute BoNT-A may increase the possibility of an anaphylactic reaction.

The effect of epinephrine 1:100,000 on onabotulinumtoxinA efficacy was tested in 14 subjects treated and evaluated for up to 6 months. The authors concluded that the onset of action and the short-term efficacy of onabotulinumtoxinA for the treatment of periorbital rhytides could be enhanced by epinephrine (Hantash and Gladstone 2007). There are other papers reporting authors' personal experience recommending the addition of epinephrine to saline for the reconstitution of abo- or onabotulinumtoxinA (Redaelli and Forte 2003; Le Louarn 2001).

Sterile Water

If sterile water is used to dissolve BoNT-A, it will work but, on the other hand, causes intense short-lived pain at the injection site (Moore and Naumann 2003).

Foam During Reconstitution

Initially, onabotulinumtoxinA was considered very fragile (Binz and Rummel 2009; Klein 1998). However many studies following anecdotal observations confirmed the persistence of its activity in different situations (Trindade de Almeida et al. 2003; Hexsel et al. 2003; Gartlan and Hoffman 1993; Jabor et al. 2003; Greene 1993; Sloop et al. 1997; Thomas and Siupsinskiene 2006).

Toth and colleagues performed several in vitro tests to evaluate the stability of fragments of BoNTs (light chain and the binding domain of the heavy chain) in response to mild agitation (Toth et al. 2009). Endogenous trypsin-like protease was used to cleave the 150-kDa toxin into a

50-kDa N-terminal light chain (Lc) and a 100-kDa C-terminal heavy chain. The latter was further proteolyzed into a 50-kDa N-terminal membrane-spanning domain (Hn) and a 50-KDa C-terminal receptor-binding domain (Hc). Then, stability parameters of isolated Lc and the binding domains Hc of BoNT to mild agitation were investigated. The authors concluded that the recombinant light chains of serotype A (LcA) rapidly lost their secondary structures and that mild stirring denatured Hc domains, but denaturation was completely prevented by the addition of nonionic detergents. They also speculated that rapid exposure of hydrophobic residues by mechanical agitation caused surface denaturation of the BoNT domains.

The effect of onabotulinumtoxinA after vigorous agitation (continuous inversion and straightening of the vial, 30 times per minute) for up to 6 weeks was evaluated in another experimental study. In this trial, 1U of the agitated onabotulinumtoxinA was injected intraperitoneally in 8 mice on days 1, 3, 5, 7, 14, 21, 28, and 42. The death of the mice was the main outcome measure, demonstrating toxin efficacy. When the study finished, half of each group of mice (4/8) died within 48 h of the injection (range 16–48 h), and the authors concluded that the effect of onabotulinumtoxinA is maintained even when it is vigorously shaken for up to 6 weeks (Shome et al. 2010).

In a clinical setting, muscle paralysis was compared in a split-face study by Almeida and colleagues in which onabotulinumtoxinA was gently reconstituted without foam formation and injected on one side of the face (periocular and glabellar areas), and onabotulinumtoxinA rapidly reconstituted with formation of as many bubbles as possible was applied to the other side. They concluded that the product's potency or short- or long-term effects were not affected by the presence of foaming during the reconstitution process (Trindade de Almeida et al. 2003).

Furthermore, an onabotulinumtoxinA consensus published in 2004 concluded that this report supports clinical experience, suggesting that the fragility of BoNT-A is not as problematic as previously reported (Carruthers et al. 2004).

Another split-face study was conducted by Kazim and colleagues. Gently reconstituted onabotulinumtoxinA was injected in half of the forehead of seven randomly selected patients, while the other half received vigorously reconstituted onabotulinumtoxinA (placed on a Vortex Touch Mixer at maximum speed for 30 s). They found no difference in effect and duration between sides (Kazim and Black 2008). The difference in results between in vitro (Toth et al. 2009) and in vivo studies might be explained by the fact that the associated proteins inside the complex of onabotulinumtoxinA might serve to stabilize the neurotoxin molecule and protect it from degradation (Trindade de Almeida et al. 2003; Shome et al. 2010; Kazim and Black 2008).

Storage

The storage of reconstituted BoNT-A vials is still controversial. Manufacturers recommend administration within 4–24 h after reconstitution (Botox 2010), storage temperature from 2 °C to 8 °C (in the refrigerator), and not freezing after reconstitution^{-20}, but several publications suggest that these recommendations may be excessively strict.

The rimabotulinumtoxinB storage temperature must be from 2 °C to 8 °C (Myobloc 2009), and there is no significant loss of activity for up to 30 months under refrigeration, although at room temperature (25 °C), it drops to at least 9 months, according to Seller (Setler 2000).

Shelf Life After Reconstitution

Reconstitution with nonpreserved saline up to 6 weeks before use was demonstrated in a multicenter, double-blind study. In 88 patients treated for glabellar frown lines, there was no efficacy reduction for up to 4 months (Hexsel et al. 2003).

Similar clinical results were found by Lizarralde et al., in which thirty patients were injected for external canthus dynamic lines with onabotulinumtoxinA reconstituted 1 week before its use compared to freshly reconstituted toxin (Lizarralde et al. 2007).

Furthermore, in the 2004 consensus panel, 73% of panelists stored onabotulinumtoxinA for more than 4 h (Carruthers et al. 2004).

In addition, onabotulinumtoxinA used after 2 weeks of refrigeration had no changes in time of onset or efficacy in the treatment of lateral orbital rhytides (Hui and Wendy 2007), and loss of efficacy in onabotulinumtoxinA vials reconstituted for up to 6 weeks before use was not found in a recent experimental trial in mice (Shome et al. 2010).

A consensus panel in 2010 concluded that reconstituted abobotulinumtoxinA can be used within 2–3 weeks without adverse effects (Kane et al. 2010). Besides this, no difference in safety or efficacy was found in a study with abobotulinumtoxinA reconstituted 2 weeks before injection in 105 patients (Hexsel et al. 2009).

Fresh or Frozen

Loss of efficacy when onabotulinumtoxinA was frozen for longer period than 2 weeks was found in animal models by Gartlan and Hoffmann (1993) and Jabor and colleagues (2003). Greene's opinion that the frozen toxin remained effective for several weeks was similar to clinical study results that found no loss of activity or additional side effects for up to 8 weeks. He also argued that in vitro experiments may not reflect clinical practice (Greene 1993; Sloop et al. 1997; Thomas and Siupsinskiene 2006).

Reconstituted and frozen onabotulinumtoxinA for up to 6 months versus OnaA not frozen and used within 4 h after reconstitution was compared in 118 sites of 80 patients by Parsa and colleagues. Their conclusion was that reconstituted onabotulinumtoxinA may be frozen, thawed, and injected without losing its potency for up to 6 months (Parsa et al. 2007), conclusions consistent with anecdotal reports from several injectors (Kane 2007).

The muscle and nerve ultrastructural alterations after injection of fresh versus stored onabotulinumtoxinA were evaluated using electron microscopy. Toxin freshly reconstituted or stored for 2 weeks under refrigeration was injected in 15 rabbits and had muscles and motor nerves harvested at 5 days and 12 weeks. No differences were found at the 5-day evaluation. However, the group that used stored toxin showed less severe atrophic changes in the muscle at 12 weeks, whereas no differences were encountered on nerve evaluation (Elmas et al. 2007). In addition, Shome and colleagues did not find loss of efficacy in onabotulinumtoxinA vials reconstituted and kept refrigerated for up to 6 weeks before use in the same experimental trial in mice cited above (Shome et al. 2010).

In a prospective, double-blind, randomized controlled trial with 40 subjects treated for horizontal forehead rhytides, Yang and colleagues found no difference in potency or duration of efficacy between abobotulinumtoxinA after 2 weeks of refrigeration or freezing and freshly reconstituted abobotulinumtoxinA (Yang et al. 2008).

Sterility

Sterility assessment is an important issue that some authors have addressed due to storing and reusing reconstituted toxin for a period of weeks has become a frequent practice.

A study simulated the routine storage and extraction methods performed in clinical practice, evaluating 127 vials of onabotulinumtoxinA reconstituted using preservative-containing saline, stored, and reused. Contamination was not evidenced in sterility analysis, although each vial underwent an average of 4.5 access procedures during a period of up to 7 weeks (Alam et al. 2006).

Eleven consecutive bottles of abobotulinumtoxinA left for 4 h at room temperature were analyzed by Menon, and no microbial growth was noted (Menon and Murray 2007). When this product was kept refrigerated for 15 days after reconstitution, the same results were found in eight vials (Hexsel et al. 2003).

Dilution Issues

The effect of dilution of BoNTs on clinical efficacy, duration, or diffusion is subject of considerable discussion. The onabotulinumtoxinA and incobotulinumtoxinA package inserts recommend dilution of 100U in 1–8 mL of saline (12.5–100 U/mL) (Botox 2010; Xeomin 2010). AbobotulinumtoxinA 300U can be diluted in 0.6–2.5 mL (120–500 U/mL) (Dysport 2009). The dilution of rimabotulinumtoxinB can be as

much as six times using normal saline, but a more concentrated solution cannot be generated (Moore and Naumann 2003; Setler 2000; Sadick 2004; Callaway 2004).

Higher dilutions, unsatisfactory results, or shorter duration was believed to be associated with greater risk of diffusion to unwanted sites by many authors (Haubner 2009; Francisco 2004; Klein and Kreydenb 2002; Bakheit 2006; Carruthers and Carruthers 2009; Wollina and Konrad 2005; Mantel 2004; Shin et al. 2000), but this is not unanimous in the literature.

Indication (Patient Selection) and Contraindications

During patients' treatment preparation, it is important to address and respect any safety concerns they might have as well as explain exactly what to expect during and after treatment.

Physicians should be prepared to listen to patients and to evaluate their psychological profile. They should be informed about all BoNT-A-related issues like application procedure, duration of clinical effects, retreatment intervals (after 4–6 months), safety history of cosmetic use, available alternatives, as well as possible adverse effects and their management. It is also necessary to determine the patients' expectations and whether they are realistic and achievable. The patient's understanding about the effects and limitations of the procedure is one of the most important points of the treatment, identifying contraindications and unrealistic expectations. For this reason an informed consent form must be presented and signed at this moment.

Before and after standardized photographs are also relevant. When shown, the follow-up visit will allow the perception of improvement objectively and also allow a register of clinical response.

Contraindications to BoNT procedure include (Myobloc 2009; Botox 2010; Dysport 2009; Prosigne 2005; Xeomin 2010; BTXA 2015):

- **Pregnancy:** botulinum toxin is classified as category C by the *Food and Drug Administration* (FDA). Although some reports of normal pregnancies and deliveries after botulinum toxin treatment have occurred, its risk could not be discarded.
- **Breastfeeding:** it has not yet been determined if BoNT-A is excreted through breast milk.
- **Preexistent neuromuscular diseases:** Individuals with peripheral motor neuropathic diseases, amyotrophic lateral sclerosis, or neuromuscular junction disorders (e.g., myasthenia gravis or Lambert-Eaton syndrome) should be monitored when given botulinum toxin. Patients with neuromuscular disorders may be at increased risk of clinically significant effects including generalized muscle weakness, diplopia, ptosis, dysphonia, dysarthria, severe dysphagia, and respiratory compromise from therapeutic doses of BoNT-A. Investigation of previous Bell's palsy is also important as this patient with peripheral facial palsy presents partial denervation and has fewer synapses in the neuromuscular junctions. Getting advice from a neurologist before cosmetic use of BoNT-A in patients with any neurological disease is recommended.
- **Any signs of infection in the site of injection**
- **Drug interactions:** substances that interfere with the neuromuscular junction through different mechanisms are supposed to interact with BoNT-A and alter its behavior. For the other hand, many of them are commonly used in dermatology, such as D-penicillamine, chloroquine, hydroxychloroquine, cyclosporine, and aminoglicosyde antibiotics (gentamicin, kanamycin, and streptomycin). These drug interactions do not constitute an absolute contraindication, but it is necessary to be careful and ponder the risks and benefits of a concomitant administration and be aware of possible complications.
- **Hypersensitivity reactions:** BoNT-A must not be used in patients with hypersensitivity to any of its components (botulinum toxin A, human albumin, and saline solution). This is an absolute contraindication.
- **Nonresponsive individuals:** patients who do not respond to BoNT-A treatment are not rare. This lack of response may be primary (genetically determined) or secondary to neutralizing

antibodies. These individuals, as long as correct doses and techniques were used, should be discouraged from subsequent treatments with BoNT-A.

Cosmetic Indications

Facial

Glabellar Region

The frown wrinkles, localized in the glabellar region, result from the contraction of various muscles: corrugators, procerus, and the medial part of the orbicularis oculi (Bentsianov and Blitzer 2004; Salashe et al. 1998). It is necessary to pay attention not only to wrinkles but especially to the pattern of the glabellar contraction and concentrate the dose in the muscles responsible for the identified movement (de Almeida et al. 2012).

One or two lines between the eyebrows mean the predominance of the corrugators' action: approximate and descend the eyebrow. Horizontal lines in the upper nose mean the predominance of procerus' action, a superficial muscle with vertical fibers localized between the nasal and frontal muscle whose contraction descends the medial portion of the eyebrows (Carruthers and Carruthers 2007; Asher et al. 2010; Hankins et al. 1998). Furthermore the radial wrinkles in the inner surface of the eyelids result from the orbicularis oculi contraction: its medial fibers when in contraction promote eyebrows' approximation and depression, contributing to the glabellar wrinkles (Carruthers and Carruthers 2007; Asher et al. 2010; Hankins et al. 1998).

Frontal Region

The frontalis muscle contraction raises the eyebrows and causes wrinkles on the forehead. This muscle is the only elevator of the upper face, surrounded by several depressors muscles (Bentsianov and Blitzer 2004; Salashe et al. 1998). For this reason its treatment is often associated to one or more of the depressors to prevent eyebrows descent (Ahn et al. 2000; Huilgol et al. 1999; Huang et al. 2000).

The current recommendation is to use smaller BoNT-A dosage than that used in the past, in order to achieve muscular relaxation rather than paralysis. Moreover, sometimes no treatment at all is preferable. The application technique consists of injection points 2 cm apart from each other, distributed in one or two horizontal lines that are placed 2 cm above the orbital rim. When lifting female eyebrows is the aim, less units or no injection is required in the lateral part of the muscle. For the other hand, in male patients, the frontalis muscle should be treated from side to side to avoid lateral elevation or "quizzical" eyebrows (Asher et al. 2010; Ahn et al. 2000; Huang et al. 2000).

Residual forehead wrinkles may be allowed in cases of first treatment or in those patients with eyebrow ptosis and compensatory frontalis contraction, if this situation is explained before the procedure.

Periorbital Region (Including Hypertrophic Orbicularis)

The periocular dynamic wrinkles known as "crow's feet," appear as two or more radiated lines located at the lateral aspect of the eyes. They result from the lateral contraction of the orbicularis oculi muscle (Bentsianov and Blitzer 2004; Salashe et al. 1998).

Relaxation or immobilization of parts of this muscle will elicit several effects: disappearance or alleviation of crow's feet lines, when its lateral portion is treated; lateral brow elevation, when the superolateral quadrant is relaxed; and also enhancement of the eye aperture when the pretarsal region is addressed (Ahn et al. 2000; Huilgol et al. 1999; Huang et al. 2000; Carruthers et al. 2007).

Perioral Region

The orbicularis oris is a sphincter muscle whose contraction causes radial wrinkles around the mouth (Bentsianov and Blitzer 2004; Salashe et al. 1998). They should be relaxed with low BoNT-A doses per lip quadrant, superficially injected in two or more sites. When the aim is labial eversion, the injection should be performed in the vermillion border (Semchyshyn and Sengelmann 2003; Carruthers and Carruthers

2003; Atamoros 2003). The perioral region is very sensible to BoNT-A. This way each unit should be carefully considered before injection, to avoid alterations in local dynamics.

Mental Region and "Marionette Lines"

Some patients present a semilunar fold and/or multiple depressions ("peau d'orange"aspect) during lower face animation. The repeated contraction of mentalis muscle is responsible for these alterations that are also associated to chin retraction (Bentsianov and Blitzer 2004; Salashe et al. 1998).

The downturn of the outer labial border occurs after contraction of the depressor anguli oris. With repetition, aging, and loss of support, it induces the formation of the known "marionette lines." The latter gives a sadness look and aged appearance to the lower face (Carruthers and Carruthers 2003; Atamoros 2003).

All these effects are amenable by BoNT-A injections.

Extra-Facial

Platysma

The platysma is a very thin and superficial muscle that covers the neck and interdigitates with the lower face musculature. Its repeated contraction causes two types of alterations: platysmal bands, resulting from the muscle fiber separation and hypertrophy in the major strength areas, and horizontal lines located in regions of high muscle adherence to overlying dermis (Bentsianov and Blitzer 2004; Salashe et al. 1998; Brandt and Bocker 2001; Brandt and Bellman 1998). Both alterations may be treated by BoNT-A.

Focal Hyperhidrosis

BoNT blocks the release of acetylcholine in all cholinergic fibers, including the autonomic nervous system ones. For this reason, it has been used as a therapeutic option in cases of localized primary or secondary hyperhidrosis, hypersalivation, crocodile tears, and Raynaud's phenomenon (Grunfeld et al. 2009; Kreyden 2006; Talarico Filho et al. 2007). Some of these indications will be addressed in a specific chapter in this book.

Side Effects and Their Managements

BoNT-A has been used as a therapeutic agent since the late 1970s. Although small amounts may briefly circulate in blood after administration, raising concerns about systemic adverse effects, the long-term follow-up in several medical areas reinforces the safety of this drug (Klein 2003, 2004). Electromyographic evidence of neuromodulator distant effects has been reported in patients treated for blepharospasm and cervical dystonia, although these findings reached no clinical significance (Singer and Weiner 1993). Nevertheless, since it is used as a therapeutic agent, there have been no reports of objective generalized weakness after routine and recommended doses.

Generally, secondary botulinum toxin injection adverse effects are mild and transitory. Bruise, swelling, and the injection site discomfort may occur. Flu-like symptoms and headache were also described (Klein 2003, 2004; Singer and Weiner 1993).

The major complications appear when BoNT reaches adjacent muscles by diffusion or migration. Usually they are infrequent and include: eyelid and eyebrow ptosis and asymmetry, diplopia, asymmetric smiles, dry mouth, etc. Other occurrences are swelling appearance in the lower eyelids caused by reduction in local lymphatic drainage after reduction of muscle activity (Klein 2003, 2004; Singer and Weiner 1993; Sommer 2003).

Eyelids ptosis is secondary to toxin diffusion to the orbital septum reaching the upper eyelid levator muscle. It may occur after the glabellar or orbicularis oculi treatment and may last for 2–4 weeks before spontaneous recovery. In severe cases, apraclonidine 0.5% (an alpha adrenergic drug used as eye drops) may be used. Its mechanism of action consists in Muller's muscle contraction, upper eyelid retraction, and enhancement in eye opening. The recommended dose is one

drop in the affected eye, 3–4 times a day for 2–4 weeks (Fagien 2004).

Smile asymmetry may occur after diffusion of BoNT-A treatment to several muscles: zygomatic major (lip elevator) from injection of lower fibers of orbicularis oculi muscle, rizorious from masseteric muscle treatment, and also depressor labii inferioris from mentalis and/or depressor anguli oris injection (Fagien 2004).

To prevent most of the described adverse events, it recommended the use of concentrated solutions and the lower effective dose in order to avoid toxin diffusion to unwanted sites and muscles (Klein 2003, 2004; Singer and Weiner 1993; Sommer 2003; Fagien 2004).

Take-Home Messages

- Botulinum toxin (BoNT) produces chemodenervation of muscles by inhibiting acetylcholine release on the neuromuscular junction.
- BoNT formulations are not identical or interchangeable: they possess individual potencies, and attention is required to ensure proper use and avoid errors.
- Each product is prepared in a different way (manufacturing, lab protocol, and clinical trials), having individual potencies and characteristics.
- BoNT injection weakens and relaxes muscles and has been used cosmetically to treat hyperfunctional and hyperdynamic lines and wrinkles. Besides, it may improve lower facial and neck contour and can also be used to treat autonomic disorders.
- Unwanted side effects are usually caused by BoNT diffusion to adjacent muscles and can be prevented by using careful technique, recommended doses, and concentrated solutions.

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Fillers

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Abstract

Injection of fillers is one of the most common procedures in dermatology. They are used to reduce fine lines, deep wrinkles, folds, and scars. They are also indicated to volumize and fill special anatomical areas on the face and body. There are many different substances for different indications, and the physician must be prepared to choose the right one according to the indication. This chapter is going to describe filler's classification, characteristics, properties, and indications. The procedure with different aspects of techniques and its indications are going to be discussed. Side effects are going to be discussed in a separated chapter.

Keywords

Injectable filler • Soft tissue fillers • Hyaluronic acid • Calcium hydroxylapatite • Poly-L-lactic acid • Polymethylmethacrylate

Contents

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Introduction

Over the last decades, the interest in aesthetic procedures is increasing with the aim to restore, maintain, and beautify the appearance. The desire for rejuvenation walks hand by hand with mankind since the beginning, with costumes, accessories, facial painting, and others. Not only, in many cultures, we can find references to accomplishment of the greatest dream, the eternal youth. Moved by this thought, physicians developed different treatments and techniques to reduce wrinkles and laxity, and the fillers are one of the most used in last years.

The perfect product to fill should be safe, biocompatible, nonteratogenic, noncarcinogenic, and not susceptible to infection. They also should stimulate a minimal immune response, not migrate, last for a long time, produce soft and natural results, and be inexpensive and easy to use and to store (Carruthers et al. 2009).

With all these topics in mind, scientists and manufactures began the process, trying to create the perfect filler. In the last years, different products were used with this purpose and some of them are being injected until nowadays. Unfortunately, some of the first fillers were prohibited because of severe complications that appeared after some days to years of their applications. Disfigured faces and even deaths were reported as consequence of the procedure.

Nowadays, some substances are approved to be used worldwide, with excellent efficacy and very few side effects. The dermatologists should know all the characteristic of the substance and have good practice with the filler to indicate and apply it correctly, avoiding side effects.

History of the Fillers

Chemical agents were used for facial augmentation, shortly after the syringe invention. In 1830, a material created by the dry distillation of beechwood tar named paraffin was the first substance used as filler (Goldwyn 1980). Unfortunately, some complications occurred few years after initial treatment, as cerebral embolization, migration, granuloma formation, and infection, and after that, paraffin was abandoned (Kontis and Rivkin 2009; Glicenstein 2007). Similar products, such as vegetable oil, lanolin, mineral oil, and beeswax, were used as filler in the subsequent years but also were abandoned due to the high risk of complications.

In the twentieth century, autologous fat has become the most common substance used for restoration of the faces (Kontis and Rivkin 2009). It is perfect for large volumes, but not to fine lines and acne scars because of its viscosity. The first report about fat transfer to correct defects in the face was done in 1876, and different techniques have been used since then. In the last years, it has been reported that superficial dermal and submucous injection of autologous fat implant promotes collagen synthesis (Coleman et al. 1993). After the 1990s, new fillers were started in the market, and autologous fat implant has become a second-choice substance for filling faces (Klein 2006). Nevertheless, fat grafting still offers some undeniable benefits, the greatest one being cost-effectiveness as the physician does not need to count each costly syringe of filler placed into the face (Lam 2015).

In the middle of the twentieth century, purified synthetic polymers in the form of injectable silicone seemingly promising in filler aged faces. Similar complications or granuloma formation has caused the FDA to ban this material as filler for aesthetical proposes, but it is still approved for ocular injections, although microdroplet injection of limited amounts of silicone material is still used today as an off-label use for this substance (Barnett and Barnett 2005).

The next tested substance as a soft tissue filler was a synthetic polytetrafluoroethylene polymer, but it was quickly abandoned because of the inflammatory reaction and difficulty of its injection (Ginat and Schatz 2013).

None of these previously attempted facial fillers had received FDA approval until the bovine collagen, in July 1981 (Klein 2006). After this point, widespread research, development of other fillers, and the renewed interest and

utilization of autologous fat happen (Attenello and Maas 2015). Despite all the researches, bovine collagen was the only FDA-approved filler until 2003, when this organ approved the first hyaluronic acid (HA) dermal filler (Restylane; Galderma, Ft. Worth, TX). Since this approval, we have seen a dramatic increase in the number of FDA-approved facial fillers in response to the growing popularity of minimally invasive facial rejuvenation procedures. Over two million soft tissue filler procedures were performed in the United States in 2014 (Surgeons ASoP 2014). Nowadays, HA has been the most used filler agent as a result of its safety, reliability, reversibility, and relatively long duration of action (Kontis and Rivkin 2009; Newman 2009).

Polyacrylamide is a biocompatible and nonabsorbable hydrogel consisting of 97.5% nonpyrogenic water and 2.5% cross-linked polyacrylamide without any additives. It is homogeneous, stable, and not biodegradable and has favorable tissue-like viscosity and elasticity. The gel is highly biocompatible and is being used in plastic and aesthetic surgery and in the production of soft contact lenses and in ophthalmic surgery in the last 20 years. Aquamid was authorized for sale in Europe in March 2001, and since then it has been used extensively for soft tissue augmentation and body contouring. Polyacrylamide gel is currently approved in several countries in Europe, Asia, the Middle East, and Latin America but is not available in the United States, although a 12-month efficacy and safety clinical trial was performed there (Narins et al. 2010). Many studies have supported the usage of Aquamid or Bio-Alcamid for the treatment of various rhytides, facial contouring, and correction of human immunodeficiency virus (HIV) lipoatrophy (Yamauchi 2014). There have been reported some cases of inflammation, nodule, granuloma formation, and delayed hypersensitivity reactions. In some instances, surgical extraction of the polyacrylamide product was necessary to correct the adverse event of nodule formation. Careful attention to injection technique and sterile precautions are necessary to minimize unwanted reactions, as this type of gel is expected to support a possible bacterial infection by low-virulence bacteria, normally present in the skin, hair follicles, and mucous membranes that may be introduced into the gel during injection (Christensen 2009). In addition, there have been recent recommendations for the usage of prophylactic antibiotics to minimize complications from bacterial injections and biofilm formation when injecting Aquamid (Yamauchi 2014).

The US Food and Drug Administration (FDA) specifically defines a cosmetic injectable device as a product used to improve appearance and does not impart any health benefits. For this reason, the FDA assigned trade names to describe the different formulations of injectable fillers. Nowadays, FDA-approved temporary fillers are collagens, HA, CaHA, and PLA, while the only permanent filler with FDA approval is polymethylmethacrylate (PMMA). Silicone, although used for certain ophthalmic conditions, is not FDA approved for any cosmetic injection (Kontis 2013).

Selecting an appropriate implant requires a thorough understanding of the materials available and the etiology of the wrinkle. Fine and superficial rhytides respond best to intradermal injection of smooth filler. Deeper wrinkles and loss of volume are best approached from the subcutaneous and periosteal space with a stiffer substance. So, physicians must analyze the face characteristics of each patient very calmly, know the effect of the different products, and be secure in treating with cannulas and/or needles depending of the indication of the procedure, to do the best treatment.

Indications

The use of dermal fillers has many different indications nowadays. Wrinkle correction is still the most common one, but laxity, scars, and loss of volume are being done even more each day. Also, it is possible to correct, reshape, and use soft tissue augmentation according to the individual needs (Carruthers et al. 2009). All this indications for the treatment with fillers on the face and body susceptible to aging modifications are listed in topics in the Table 1.

Table 1 Indications for the treatment with fillers

Indications to soft tissue filler	
Nasolabial folds	Forehead rejuvenation
Melomental folds	Perioral rejuvenation
Midface folds	Lip augmentation
Glabella	Chin augmentation
Eyebrow shaping	Mandibular augmentation
Tear troughs	Nasal contouring
Temporal hollows	Earlobe rejuvenation
Acne scarring	Hand rejuvenations
Scar contouring	Breast rejuvenation

Patient Selection and Pre-procedure Evaluation

A complete anamnesis should be done in the first visit paying close attention to the past history of allergies, herpes, side effects with other invasive procedures or plastic surgeries, disorders of coagulation, not controlled hypertension, or diabetes. Skin infections in the area to be filled should be treated before, and patients with past history of herpes should use prophylactic antiviral medications 1–2 days before the procedure, completing the 5 days of treatment with therapeutic doses. Patients should also be instructed to avoid substances as acetylsalicylic acid, vitamin E, *Hypericum perforatum*, and nutritional supplements such as ginkgo biloba, garlic, ginseng, and others that may affect coagulation for 2 weeks before the procedure (Small and Hoang 2012). The risks of side effects and possible complications associated with proposed treatment and anesthesia should also be discussed and exposed to the patient through an informed consent form, which must be signed before scheduling the procedure.

The physical examination is essential to evaluate the face and check if it corresponds to the patient's complains. The literature describes scale of aging and reports the symmetry of lines and angles of a perfect face. Also many authors have described different techniques of evaluating the patients finding the correct point to be filled. These descriptions facilitate the analyses of the application, but the physician has to learn how to understand what each patient needs individually. There is no rule to fill the same area exactly in the same way in different patients, and only the experience can make it possible to be understood (Shoshani et al. 2008).

Physicians should explain the limits of each treatment and construct real expectations about the procedure and possible results. Sometimes, treatment should be done in more than one visit if patient is insecure.

A photographic register must always be performed before and immediately after procedure. This is very important not only to comparison (before and after photography) but also to show unusual findings such as preexisting asymmetries which patients had not been realized before.

Procedure

Aseptic and Antiseptic Care

Before injection, the skin should be cleaned with an antibacterial soap or alcoholic solution (2–4% of chlorhexidine digluconate). In the case of topical anesthesia, the same antibacterial substance must be reapplied to remove the product. Aqueous solution of chlorhexidine 0.2–1% could also be used if preferable. All materials used by the physician, such as gloves, gauze, needles, cannulas, and syringes, prepared with the products must be sterile. The physician should take care to keep the procedure sterile until the end.

Anesthesia

Effective pain management starts prior to the procedure. A relaxed and confident patient will require less anesthetic medications than an anxious one. An adequate anesthesia is essential to perform comfortable treatment of the patient. Preferentially the anesthesia should lead to minimal distortion of area to be treated in order to maintain the normal proportions of the face. Topical anesthesia, troncular anesthesia, or very

small-volume local infiltration is preferred. Ice and other cooler devices can also be used to make the punctures of the injection more comfortable for the patients. To choose the anesthetic method, physician must think of the sensibility of the treated area (e.g., lips), the patient tolerance to pain, and the need to preserve initial anatomy of the region. Patients treated for the first time with fillers usually are more anxious and sensible and would benefit a lot if a good method of anesthesia was used.

Actually, some dermal fillers are now available with lidocaine and hyaluronic acid products are the most frequent one with this advantage. Also, calcium hydroxylapatite and polylactic acid should be mixed with 2% lidocaine.

Technique of Application

A variety of injection techniques have been reported. The average dose injected depends on the indication and the type of product chosen (Carruthers and Carruthers 2005a). Injection techniques depend on the physician experience, the anatomic site of treatment, the material chosen for the treatment, the viscosity of the product, and final goals of procedure. Some examples of these techniques are summarized in Table 2.

There are several different techniques to obtain the best results for each region in each patient (Fig. 1). Four of these techniques have been employed more than the others: retro-injection, fern technique, network or cross-hatch, and bolus. The serial puncture technique is very effective for more superficial levels of the mid to upper dermis and is used for correcting fine wrinkles (Kim and Sykes 2011). The linear threading technique involves the uniform deposition of the filler substance, while the needle is slowly withdrawn (retro-injection) or advanced (antero-injection). Nasolabial folds and lips can both be treated with this technique (Kim and Sykes 2011; Lee and Kim 2014). The fanning technique and the cross-hatching technique are effective to distribute filler substance over a wide surface. Other kinds of technique considered when facial augmentation and remodeling are the final goal are bolus, tower, and layer techniques (Kim and Sykes 2011; Lee and Kim 2014). Physicians must have special attention in do not inject filler too deep when the "problem" is superficial, to achieve optimal results with less amount of products. The bolus technique consists on delivering the product at a deep layer in a unique point, subcutaneous or supraperiostal, introducing the needle in a perpendicular angle with the skin. In a similar technique, the tower technique, the needle is placed in the same perpendicular angle with the skin, reaching deeper layers, and the filler is placed as the needle is withdrawn, crossing multiple layers, creating a sustention tower to the soft tissue (Humphrey et al. 2015).

Table 2 Different techniques of application of the fillers

Technique of application	
Serial puncture technique	Retro-injection
Tunneling	Supraperiosteum depots
Fern technique	Vertical tower
Microdroplets	Network or cross-hatch
Antero injection	Bolus

The physician could use needle or a blunt-tip microcannula to do the procedure, and its choice depends on the region to be treated and its experience (Sundaram et al. 2012). Needles are popular (23–32 gauge), but there is some argument for the use of cannulas in the prevention of hematoma and vascular compromise (Braz and Sakuma 2012). The use of microcannulas for injection of alloplastic fillers began 5–6 years ago, after several years of experience of the instrument for injection of autologous fat. The entry point for the blunt microcannula is first made with a shaper "pilot" needle, and then the microcannula is carefully inserted and maneuvered until the desired tissue plane is reached. The use of this device is associated with an improve of safety and decreased risk of ecchymosis leading to faster return to normal daily activities and, also, an improve of comfort during injection (Sundaram et al. 2012; Ballin et al. 2015).

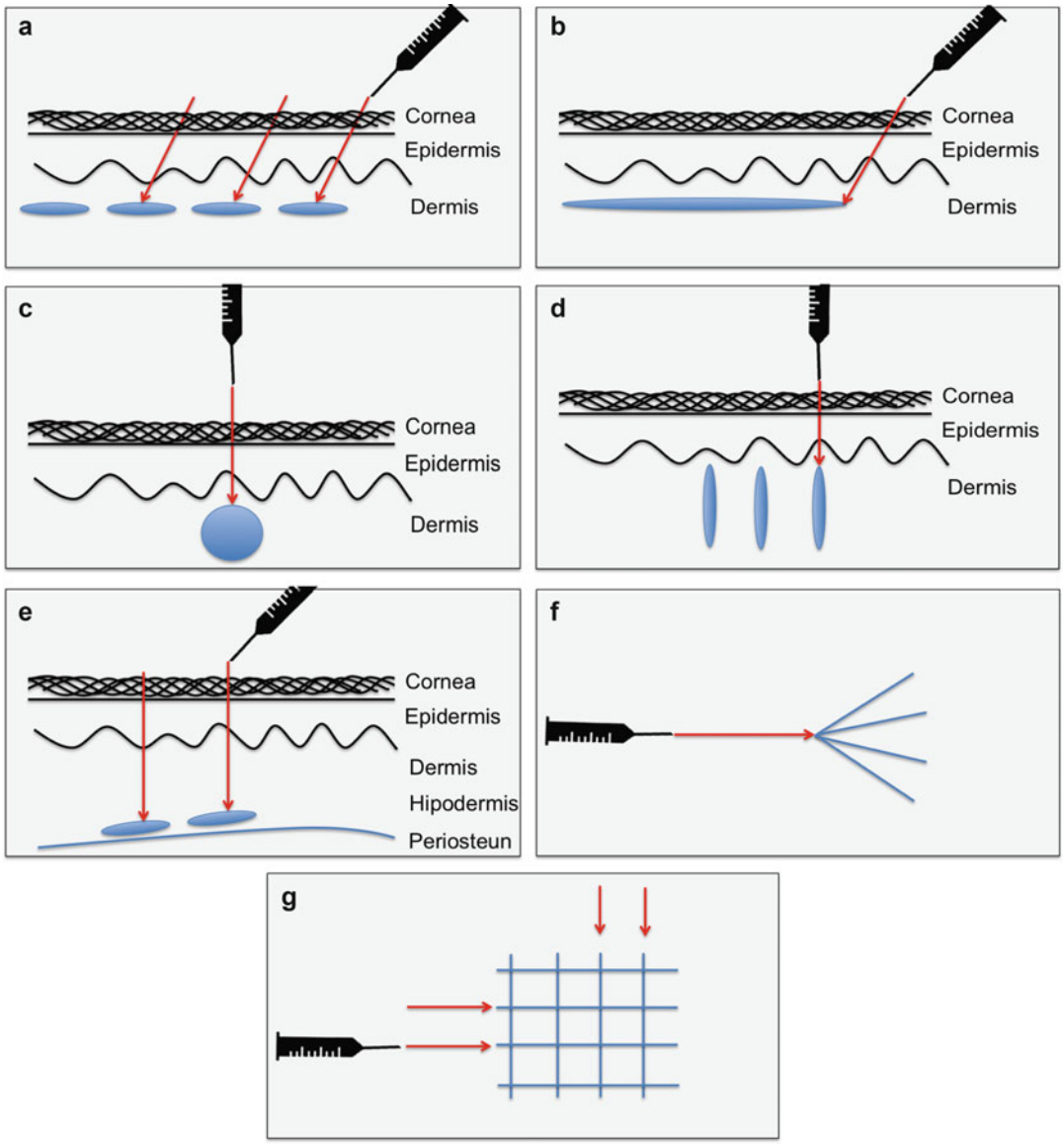

Fig. 1 Techniques of applications. (**a**) Serial puncture or microdroplets, (**b**) linear threading or tunneling, (**c**) bolus, (**d**) vertical tower, (**e**) supraperiosteum depots, (**f**) fanning, (**g**) cross-hatching

Material

Many different methods of categorization have been proposed, based in part on the characteristics of each substance. However, no single, universally agreed upon system exists to date.

There is no universal classification system for fillers. Different classification systems have been introduced as the dermal filler market has expanded in the last years, and they have been used to varying degrees. These include classifying products according to the source of material, duration of effect, biodegradability of components, and mode of action.

As a common problem of any classification system, some products fit more neatly into

the categories than others. Current classification systems are not ideal, but they contribute to help physicians understand each product's unique characteristics. Fillers can be classified according its source, duration, biodegradability, mechanism of action, safety, and rever-sibility.

1. Source of material
   Substances can be identified according to their source as autologous, biological, or synthetic.
2. Duration of effect
   Define substances according to how long the filler maintains its effect in the region treated as temporary, semipermanent (longer lasting), and permanent.
3. Biodegradability of components
   Biodegradable fillers can be absorbed by the body and tend to have a shorter duration of effect and a lower risks for side effects. On the other hand, the nonbiodegradable fillers are compound of some substances that do not degrade and maintain an excellent result for a long time, but they tend to be associated with more frequent adverse side effects as granuloma formation.
4. Mechanism of action
   One of the proposed classification systems is based on primary mechanism of action of each material. This was first proposed by Werschler and Narurkar and has been widely used till then. In this approach, dermal fillers are placed into categories of either replacement volume or collagen biostimulation, which yield both longer-lasting treatment results and possibly other benefits to the dermis, as a primary mechanism of action.
5. Classification taking into account long-term safety and reversibility of its possible side effects (De Boulle 2004):
   Group 1. Nonpermanent and biodegradable compound:
   - Bovine collagen
   - Hyaluronic acid gel

   Group 2. Semipermanent and biodegradable compounds:
   - Polylactic acid
   - Lipocytic dermal augmentation

   Group 3. Permanent and reversible compounds:
   - Expanded polytetrafluoroethylene

   Group 4. Permanent and nonreversible compound:
   - Liquid injectable silicone
   - Polymethylmethacrylate
   - Methylmethylpolysiloxane particles

Types of Fillers

Collagen Fillers

Clinical trials with the injection of bovine collagen for age-related wrinkles were performed in 1977–1978 and the FDA approved it in 1981 (Kontis and Rivkin 2009; Fagien and Klein 2007).

There are several injectable bovine collagen brands, but three of them are the most famous ones. All of them are a white opaque gel available in a single-use glass syringe with sterilized needles of 27 or 30 gauge:

- *Zyderm family* is compound of products of purified bovine dermal collagen with lidocaine.
- *Cosmoderm* is a human-based collagen with lidocaine.
- Evolence is a porcine collagen gel and is the newest one without lidocaine.

The Zyderm family is a compound of Zyderm I, Zyderm II, and Zyplast. Bovine collagen is considered a biomaterial that is being used since 1982. They are considered to have week immunogenicity and are compounding of collagen type I (95–98%), collagen type III (2–5%), and lidocaine. The concentration of the products will lead to which layer it should be placed, as higher concentrations should be injected deeper into the skin. Prior to the procedure, it is mandatory to search for allergic response to the product performing a skin test, which should be followed by a second test to assure negativity, 2 weeks after the first one.

The development of human-based collagen was incited by the need of a product that does not demand a skin test. Based in its safety profile after the use in burns and wounds, the Cosmoderm

family was approved by FDA as filler in 2003. There are two approved presentations of the product: Cosmoderm 1 and Cosmoplast. They are very similar to Zyderm and Zyplast, except by the fact that they come from human fibroblast culture and it makes skin tests unnecessary. Patients can be treated in the very first consult.

In the late 1980s, researches began to extract human collagen fibers and acellular dermal matrix from tissue back-derived skin of cadavers and created Cymetra. This material is rehydrated with lidocaine in the physicians' office before injection and does not need a skin test in the patient, but results last for about 3–6 months. Some products compound of human collagen were commercialized but not for a long time because of some adverse side effects.

The newest products of this class, approved in 2008, are Evolence and Evolence Breeze, a long-lasting atelomeric porcine collagen gel implant that is cross-linked with the natural sugar ribose. It sets within minutes of injection and will not migrate out of the treated area, and also not require skin test.

Liquid Silicone

Liquid injectable silicone (LIS) was first used as filler in the 1950s. By that time, any form of liquid silicone has FDA approved, and it was the preferred injectable filler until collagen became available. Unfortunately, severe complications as migration and foreign body reaction due to injection of a large bolus products by untrained physicians were frequent (Jones 2011). This scenario was kept until the early 1990s, when FDA decided to ban all forms of silicone for cosmetic use. Few years later, in the late 1990s, FDA approved two new forms of highly purified liquid injectable silicone: Silikon 1000 and Adatosil 5000, for use as intraocular implants to tamponade retinal detachment. In addition, the FDA Act of 1997 made off-label uses legal. So, from that time on, liquid injectable silicone has been used as off-label treatment of soft tissue augmentation.

Liquid injectable silicone readily fulfills most of the criteria for an ideal filling substance (Orentreich 2000). It is a clear, odorless, tasteless, colorless, and stable substance. It does not harden or soften, remains unaltered within the range of human body temperature, and is chemically unchanged by exposure to air, most chemicals, and sunlight. It lacks mutagenic, carcinogenic, and teratogen effects and no true allergies to silicon have been documented. Also, it can be stored for long periods of time at room temperature and does not allow the growth of microorganisms (Barnett and Barnett 2005).

Despite all complications described in literature (e.g., tissue destruction, scarring, acute pneumonitis, granulomatous hepatitis, etc.), the long-term experience of physicians skilled in the administration of liquid injectable silicone has shown it to be safe and efficacious for soft tissue augmentation (Jones 2011; Orentreich 2000). Commonly, most granuloma-related reports are associated with impurities in the silicon and silicones associated with other substances (Barnett and Barnett 2005). The most effective and safe technique to inject LIS is the microdroplet serial puncture, defined as 0.01 ml per puncture, in the subdermis. Small volumes as 0.5 mL per puncture should be used for smaller defects and up to 2 mL for larger areas of atrophy in each session, with multiple sessions staged every month or with longer intervals (up to 3–9 months apart) (Carruthers and Carruthers 2005b). Also, physician should use a FDA-approved highly purified product.

In theory, a capsule of new collagen "encircles and holds" the microdroplets of LIS injected, in a process that goes on for approximately 3 months, and during this time, neocollagenesis adds volume to the microdroplet.

Polymethylmethacrylate (PMMA)

Polymethylmethacrylate (PMMA) is the first and only permanent filler approved by FDA for cosmetic use (Requena et al. 2011; Ahn and Kao 2014). It is a biphasic filler composed of PMMA microspheres (30–42 μm in diameter, approximately six million microspheres per 1 mL) that make up 20% of the filler volume, suspended in a carrier gel of 3.5% degradable bovine collagen, 92.6% buffered isotonic water, and other buffer

materials that make up the remaining 80% (Ahn and Kao 2014).

In 2006, the FDA approved PMMA for correcting nasolabial folds as Artefill® (Suneva Medical, Inc.). In December 2014, Artefill® has been rebranded as Bellafill® and was approved for the treatment of acne scars, and it is the only dermal filler available on the market for this indication (Ballin et al. 2015). Bellafill is a third-generation PMMA fillers, and it is a suspension of PMMA beads in a bovine collagen delivery vehicle containing 0,3% lidocaine. The beads of PMMA are not absorbed but induce fibroplasia and become encapsulated by endogenous collagen. For this reason, it should be indicated to deeper folds and rhytides and injected into the deepest dermal level or subdermis, after a skin test (Ballin et al. 2015).

It acts in two phases: in the first phase, the initial correction is provided by the bovine collagen carrier gel, which is absorbed over 1–3 months after injection and then completely replaced by the host connective tissue by 3–4 months, encapsulating the remaining PMMA microspheres; in the second phase, the PMMA microspheres, which are held in place by the encapsulation, provide a scaffold upon which the dermis can recover to its original thickness (Newman 2009; Mercer et al. 2010).

Injecting permanent filler does not signify that clinical results will last forever because the dermis changed as the patient goes through aging process. Also, the main concern about the use of permanent filler is the possibility of late-onset adverse events or displacement of the material when facial structures change with the aging process (Ballin et al. 2015).

Calcium Hydroxylapatite

Calcium hydroxylapatite (CaHA) is synthetic semisolid and biodegradable filler which trademark is Radiesse® (Merz North America, Greensboro, NC). Radiesse is consisting of 30% synthetic CaHA microspheres (diameter of 25−45 μm) suspended in a 70% aqueous carboxymethyl cellulose gel carrier. The soluble carrier gel evenly distributes the Radiesse CaHA microspheres and gradually dissipates leaving the microspheres at the injection site where they induce neocollagenesis by fibroblast activation (Loghem et al. 2015). The immediate volume correction as well as stimulation of long-term deposition of new collagen surrounding the microspheres contributes to an average duration of effect of 12–18 months, though some results have been noted 24 months postinjection. So, it is considered long-lasting or semipermanent biocompatible filler that has no antigenicity and thus provokes only a little immune response. Its composition is identical to the physiologic mineral from human bones and teeth, but no calcification or osteogenesis has been reported in extensive literature describing the use of CaHA in a variety of soft tissue applications because progenitor cells for osteogenesis do not exist in soft tissue. Over time, the CaHA microspheres are broken down into calcium and phosphate ions by the phagocytes (Loghem et al. 2015). In 2006, Radiesse received FDA approval for the correction of moderate-to-severe facial wrinkles and folds, such as nasolabial folds, and/or the correction of the signs of facial fat loss in people with human immunodeficiency virus. Since some trials were conducted in last years, Radiesse has been progressively used for a variety of aesthetic facial and hand indications (Attenello and Maas 2015; Ahn and Kao 2014; Ali et al. 2007).

Clinical results observed after 1–3 months of its injection are supported by the carrier gel, but the microparticles of smooth and round microspheres stimulate a small granulomatous reaction and then fibrosis that take the carrier gel place in the local tissue augmentation (Ahn and Kao 2014; Mercer et al. 2010; Marmur et al. 2004). After 3 months, the CaHA microspheres are unchanged and surrounded by a fine capsule of fibrin, scattered fibroblasts, and macrophages. After 6 months, a fine fibrous capsule surrounds the implant with fibroblast replacement of the aqueous gel surrounding aggregates of irregular and porous microspheres, localized in the dermis/subcutaneous junction, encapsulated by a thin fibroblastic stromal with flatted cells, and surrounded by thick collagen, histiocytes, and multinucleated

giant cells. Immunohistochemical analysis revealed a strong staining for collagen type I around the microspheres and a weak staining for collagen type III (Ahn and Kao 2014).

Clinical effects have been observed to last about 8 months after a single injection and approximately 10–12 months after multiple injections. CaHA is radiopaque and appeared on radiographs, but studies show that it was clearly distinguishable from bones and adjacent structures on CT scans in almost all patients, with no obscuration of underlying structures and no evidence of migration (Carruthers et al. 2008; Pavicic 2013). Although a higher rate of local adverse effects has been observed, such as cellulitis and nodule formation, it can potentially be seen with almost all other dermal fillers (Ahn and Kao 2014; Daines and Williams 2013).

Poly-L-Lactic Acid

Poly-L-lactic acid (PLA) is a biodegradable and bioabsorbable aliphatic polyester produced by carbohydrate fermentation of corn dextrose, synthesized by French chemists in 1952. Since then, PLA have been used in suture materials, resorbable plates, and screws in orthopedic, neurologic, and craniofacial surgery and in membranes for guided tissue regeneration in periodontal surgery. Each PLA molecule is relatively heavy (140 kDa), 2–50 μm in size, and irregularly crystalline shaped, all of which contribute to its slow physiological absorption. Injectable PLA is a biostimulator rather than a traditional filler, which provides immediate volumetric improvement, as the half-life of L-polylactides is estimated at 31 days, with total absorption occurring by 18 months (Greco et al. 2012; Athanasiou et al. 1995). It was approved as semipermanent filler for facial lipoatrophy associated with human immunodeficiency virus in 2004 and for cosmetic use in healthy patients in 2009 with the trademark Sculptra (Dermik Laboratories, Berwyn, PA) (Attenello and Maas 2015; Ahn and Kao 2014). Sculptra is a lyophilized powder of synthetic L-polymers of PLA, sodium carboxymethyl cellulose, and mannitol that must be reconstituted with a minimum of 5 ml sterile water to create a 4.5% suspension of PLA microspheres in 2.7% methylcellulose. However, it is preferable to use higher volumes of diluent, up to 10 mL per vial, to reduce the risk of nodule formation at the site of injection (Kontis 2013; Ahn and Kao 2014; Vleggaar 2006).

After injected in the subcutaneous, PLA induces a moderate inflammation and a fine capsule, macrophages, and some lymphocytes surround its microspheres in the first 3 months. After 6 months, most microspheres are porous, fissured, or deformed, and a secondary stronger inflammatory phase occurs, evidenced by the presence of macrophages and many foreign body giant cells. It elicits resorption and formation of fibrous connective tissue around the foreign body, causing dermal fibroplasia, leading to the clinical volumizing effect. After 9 months, the PLA microspheres are completely degraded and there is no remnant fibrosis. The newly formed collagen remains and results in cosmetic augmentation that lasts at least 24 months (Requena et al. 2011; Ahn and Kao 2014; Mercer et al. 2010; Greco et al. 2012; Nicolau 2007).

The safety and efficacy of PLA for soft tissue augmentation are well established, but 2–3 (or even more) treatment sessions are required for optimal facial volume restoration. Unfortunately, the main concerns about PLA injection are the delayed side effect of non-visible palpable nodules and visible papules. The "rule of 5 s" is defended to reduce the chances of these complications whereby the patient massages the area for 5 min, five times daily for 5 days after the injection (Jones 2011).

Hyaluronic Acid

Nowadays, hyaluronic acid (HA) gel is the most widely used dermal filler in the North America (Surgeons ASoP 2014). In recent years, FDA has approved some trademarks for distinctive indications they had before. In 2011, FDA approved Restylane® for submucosal lip augmentation. In 2013, Juvéderm Voluma® was approved for deep subcutaneous or supraperiosteal injection in cheek augmentation. And in 2014, Restylane® Silk was approved for perioral rhytides (Ballin et al. 2015). Nevertheless, there are still lots of off-label for HA injections as marionette lines, ear

lobes, scars, dorsum of the hands, temples, jawlines, glabella, and tear trough, for example.

Hyaluronic acid (HA) is a naturally occurring polysaccharide found in the dermis, umbilical cord, synovial joint fluid, vitreous fluid of the eye, hyaline cartilage, and connective tissues. HA is the most abundant glycosaminoglycan found in the human dermis with the same chemical structure regardless of the species and the type of tissue of origin. Also, it is an essential component of extracellular matrix of all adult animal tissues, and almost 50% of the total HA concentration in the body is located in the dermis (Kablik et al. 2009). Naturally occurring HA is a viscous liquid in its free form, and it is completely metabolized few days after injection into the skin by free radicals and enzymes naturally present in the skin such as hyaluronidase (Kablik et al. 2009). First fillers compound of HA were derived from rooster combs, but residual avian proteins caused allergic reactions in some patients. Nowadays, FDA-approved products available on the market are all derived from bacteria and via fermentation of *Streptococcus equinus* (Ballin et al. 2015). At physiologic pH, HA has excellent biocompatibility as it is anionic and thus binds to water extensively (Maas and Bapna 2009). HA dermal filler manufacturers use cross-linkers to stabilize the HA polymer and prevent degradation when injected into the skin and also to create a polymer network transforming the viscous liquid into a gel. Enzymes and free radicals can break down the chains in much smaller portions at a time because the large-size HA gel network is connected by the cross-linkers. This contributes to a slower degradation of the HA gel in the skin and to a longer persistence of its effects when used as filler. Gel fillers compounded of HA may differ by the technology of cross-linking, the amount of cross-linked HA, and the degree of cross-linking within the gel. The most common cross-linking agent used, which reacts with hydroxyl sites on the HA chains, is 1,4-butanediol diglycidyl ether (BDDE) (Edsman et al. 2012).

Based in this difference of HA gels, there have been variable histological results noted with the different types of HAs in clinical use (Flynn et al. 2011). The effect that cross-linking technology has on filler performance and the influence it has on the efficacy and durability of the filler product are well established (Jones 2012; Wohlrab et al. 2013). The harder the product gets, the better the resistance to the dynamic forces incurred with facial muscle movement, providing long-lasting support and volumization. The different possibilities of characteristics of "HA filler class" make it special and versatile as it can be injected to treat almost everything from fine wrinkles, lips, and tear trough to facial volumizing. Side effects as transitional edema and erythema are common, but nodules and blue papules (the Tyndall effect) may appear when choosing the inappropriate into the performed treatment (Attenello and Maas 2015). Fortunately, HA fillers have a unique characteristic that is its reversibility via enzymatic digestion with hyaluronidase, a FDA-approved enzyme to temporary disperse the HA filler agent (Sundaram and Cassuto 2013; Rao et al. 2014).

Some properties of these fillers are summarized in Table 3.

Post-Procedure Care

- Patients should be informed not to practice physical exercise, expose the face to heat, drink alcohol, and tan the area treated, until the swelling that can be present immediately after the injection of the filler no longer exists.
- Patients should be advised to make cold compress on the treated area immediately after the procedure to reduce the risk of bruising or swelling, except in the case of vascular obstruction signs.
- It is also a benefit to raise the headboard of the bed the night after the procedure to help reduce swelling.
- Patients should not perform self-massage on the area treated.
- Acetaminophen can be used to reduce local discomfort.
- Patients should be evaluated 4 weeks after the procedure to check the reduction of lines and wrinkles and to analyze if there is anything to complement or correct (Small and Hoang 2012).

Table 3 FDA-approved devices for dermal filler procedures: trademark, material, manufacturer, indications, and date of the decision to approve its use (Adapted from: http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/CosmeticDevices/WrinkleFillers/ucm227749.htm)

Trade name	Material	Manufacturer	Approved for (decision date)
Radiesse	Hydroxylapatite	BioForm Medical, Inc.	Restoration and/or correction of the signs of facial fat loss (lipoatrophy) in people with HIV (12/2006) Subdermal implantation for correction of moderate to severe facial wrinkles and folds (such as nasolabial folds) (12/2006) Subdermal implantation for hand augmentation to correct volume loss in the dorsum of the hands (06/2015)
Sculptra Aesthetic	Poly-L-lactic acid (PLA)	Sanofi-Aventis, USA	Use in shallow to deep nasolabial fold contour deficiencies and other facial wrinkles (07/2009)
Restylane Lyft with Lidocaine	Hyaluronic acid with lidocaine	Galderma Laboratories	Moderate to severe facial folds and wrinkles or in patients over the age of 21 who have age-related volume loss (07/2015)
Restylane Silk	Hyaluronic acid with lidocaine	Valeant Pharmaceuticals North America LLC/Medicis	Indicated for lip augmentation and dermal implantation for correction of perioral rhytids (wrinkles around the lips) in patients over the age of 21 (06/2014)
Restylane-L Injectable Gel	Hyaluronic acid with lidocaine	Medicis Aesthetics Holdings, Inc.	Injection into the mid to deep dermis for correction of moderate to severe facial wrinkles/folds (such as nasolabial folds) and for lip augmentation in those over the age of 21 years (08/2012)
Restylane Injectable Gel	Hyaluronic acid	Medicis Aesthetics Holdings, Inc.	Lip augmentation in those over the age of 21 years (10/2011)
Restylane Injectable Gel	Hyaluronic acid	Q-med Ab	Injection into the mid to deep dermis for correction of moderate to severe facial wrinkles and folds (such as nasolabial folds) (12/2003)
Prevelle Silk	Hyaluronic acid with lidocaine	Genzyme Biosurgery	Injection into the mid to deep dermis for correction of moderate to severe facial wrinkles and folds (such as nasolabial folds) (02/2008)
Elevess	Hyaluronic acid with lidocaine	Anika Therapeutics	Use in mid to deep dermis for correction of moderate to severe facial wrinkles and folds (such as nasolabial folds) (12/2006)
Belotero Balance	Hyaluronic acid	Merz Pharmaceuticals	Injection into facial tissue to smooth wrinkles and folds, especially around the nose and mouth (nasolabial folds) (11/2011)
Captique Injectable Gel	Hyaluronic acid	Genzyme Biosurgery	Injection into the mid to deep dermis for correction of moderate to severe facial wrinkles and folds (such as nasolabial folds)
Juvederm 24 Hv Juvederm 30 Juvederm 30 Hv	Hyaluronic acid	Allergan	Use in the mid to deep dermis for correction of moderate to severe facial wrinkles and folds (such as nasolabial folds)
Juvederm Voluma Xc	Hyaluronic acid with lidocaine	Allergan	Indicated for deep (subcutaneous and/or supraperiosteal) injection for cheek augmentation to correct age-related volume deficit in the midface in adults over the age of 21 (10/2013)

(*continued*)

Table 3 (continued)

Trade name	Material	Manufacturer	Approved for (decision date)
Ziplast (R)	Collagen	Collagen Corp.	Use in mid to deep dermal tissues for correction of contour deficiencies (06/1985)
Zyderm Collagen Implant	Collagen	Allergan	Use in the dermis for correction of contour deficiencies of this soft tissue (09/1981)
Fibrel	Collagen	Serono Laboratories	The correction of depressed cutaneous scars which are distendable by manual stretching of the scar borders (02/2008)
Cosmoderm I	Collagen	Inamed Corporation	Injection into the superficial papillary dermis for correction of soft tissue contour deficiencies, such as wrinkles and acne scars (03/2013)
Evolence Collagen Filler	Collagen	ColBar LifeScience l	The correction of moderate to deep facial wrinkles and folds (such as nasolabial folds) (06/2008)
Artefill	Polymethylmethacrylate beads, collagen, and lidocaine	Suneva Medical, Inc.	Use in facial tissue around the mouth (i.e., nasolabial folds) (10/2006)

Side Effects and Complications

Side effects that follow any form of skin sticking can be seen in all of these fillers as they are delivered via injection (see chapter "Fillers Complications and their Management"). These include needle marks, swelling, persistent ecchymosis, pain, itching, outbreaks of herpes, and infectious processes. Many of these complications are technique related, such as palpable or visible implants, uneven distribution, overcorrection, under correction, allergies, hypersensitivity reactions, and nodularity (permanent or transient based on the type of implant and its depth) (Duffy 2005).

The most common adverse events associated with fillers are local injection site reactions (Cohen 2008). Erythema, swelling, and bruising, which often are unavoidable, may be considered expected effects. Less frequent events include contour irregularities; product migration; bluish discoloration known as the Tyndall effect, which is more likely to occur with superficial injections, leaving a bluish discoloration due to the more strong scattering of the blue light spectrum by the colloid particles; post-inflammatory hyperpigmentation; nodules; infection at the injection site; scarring; hypersensitivity and foreign body granuloma; biofilms; and vascular occlusion, potentially leading to blindness (De Boulle 2004; Beer and Avelar 2014).

Table 4 Classification based on onset of complications

Early	<14 days
Late	14 days–1 year
Delayed	>1 year

These more severe complications often can be avoided. Appropriate skin preparation and a sterile technique are critical in preventing infections, while deep placement of filler material reduces the risk for Tyndall effect, nodules, and scarring. Skin necrosis occurs by external compression of the blood supply by the product or occlusion via direct injection into a vessel (Mansouri and Goldberg 2015).

The timing and the onset of symptoms can categorize complications resulting from injectable fillers (Kim and Sykes 2011; Table 4).

Conclusions

Most aesthetic patients prefer to avoid surgery wherever possible and seek natural-looking results. This is one of the reasons why the soft tissue implant use and the number of available

products increase around the world every year. With the increasing demand for less invasive, quick, reliable, prophylactic, and minimal downtime procedures, it is important that physicians have a thorough understanding of the soft tissue fillers available and their use and management. This chapter will provide general information about most common fillers used in the previous years.

Take-Home Messages

1. Injection of fillers is one of the most common procedures in dermatology. They are used to reduce fine lines, deep wrinkles, folds, and scars.
2. The perfect product to fill should be safe, biocompatible, nonteratogenic, noncarcinogenic, and not susceptible to infection. They also should stimulate a minimal immune response, not migrate, last for a long time, produce soft and natural results, and be inexpensive and easy to use and to store.
3. A complete anamnesis should be done in the first visit paying close attention to the past history of allergies, herpes, side effects with other invasive procedures or plastic surgeries, disorders of coagulation, not controlled hypertension, or diabetes.
4. The physical examination is essential to evaluate the face and check if it corresponds to the patient's complains.
5. A variety of injection techniques have been reported. The average dose injected depends on the indication and the type of product chosen (Carruthers and Carruthers 2005a). Injection techniques depend on the physician experience, the anatomic site of treatment, the material chosen for the treatment, the viscosity of the product, and final goals of procedure.
6. Fillers can be classified according its source, duration, biodegradability, mechanism of action, safety, and reversibility.
7. When used correctly by a savvy physician, filler injection is a very effective procedure in cosmetic dermatology, preventing and treating aging, as well as reshaping the face.

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Part VI

Special Approaches in Cosmetic Dermatology

Cosmetic Approach for Men

Daniela Alves Pereira Antelo and Maria Claudia Almeida Issa

Abstract

There are many differences between male and female patients, regarding dermatological treatments and procedures, such as facial anatomy, skin biology, and aging skin process. Sex steroids modulate skin thickness, skin surface pH, wound healing, and potencial for infection and diseases. Men's skin is usually thicker and oilier than women's. Androgenetic alopecia is the most common cause of hair loss in men, and it usually has a considerable psychosocial impact and emotional distress. Other common problems related to hair are the pseudofolliculitis barbae and superficial folliculitis on the beard area secondary to the coiled hair shafts repenetrating the skin and to the frequent habit of shaving. All these conditions should have different approach and are going to be discussed in this chapter.

Keywords

Men • Cosmetic techniques • Fillers • Toxin • Lasers; acne

Contents

Introduction

In human species, a male is attractive in a different way than female so much that to refer or to call a male "beautiful" is actually not a compliment to most males. In a common sense, males are attractive when they are powerful, intelligent, and rich. Nevertheless initial visual impression is considered

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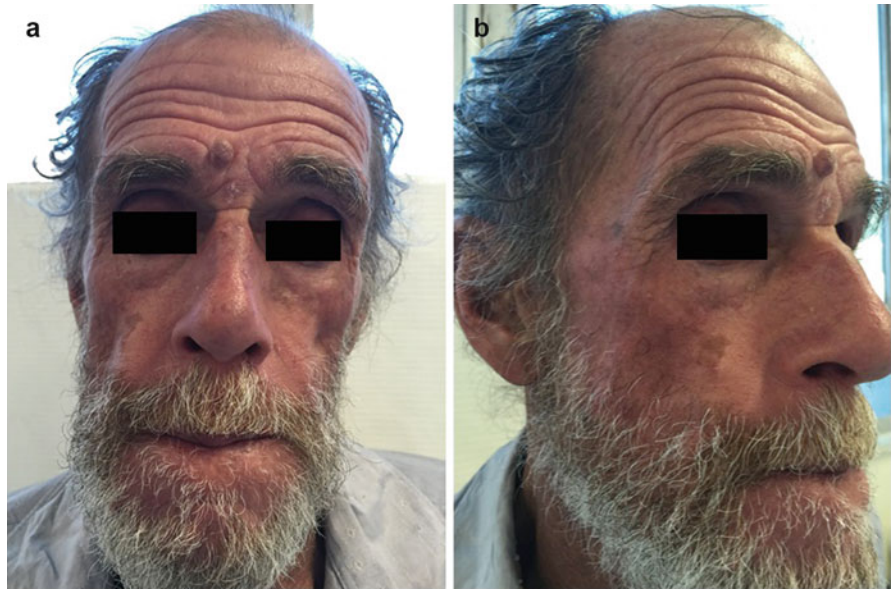

Fig. 1 Man with intense actinic damage (actinic keratosis and hyperpigmentation): chronological aging and photodamage

important in human and professional affairs even for men. Nowadays taking care of the skin and trying to look good are also becoming important to the contemporary men (Maio and Rzany 2009).

There are many differences between male and female facial anatomy, skin biology and the aging process (Keaney 2015; Oblong 2012). As aging results from multifactorial influences and also from gender distinctions, men may have different skincare regimens than women. Male skin is more sensitive to some environmental stressors such as wounding and ultraviolet radiation (Oblong 2012). Nonetheless, compliance is a big issue regarding sunscreen use in men (see Fig. 1a and b showing intense actinic damage in and old man: chronologic aging and photodamage).

In addition, men are a fast-growing group of patients at a dermatologic clinic, and some special aspects of male patients are subject of this special section. A desire to be more competitive and youthful in the workforce and the social acceptability of cosmetic procedures may contribute to the increase in male patients (Keaney and Alster 2013).

Some considerations should be taken into account when treating men. They have a tendency to avoid complex and time-consuming regimens. Men want to "fix it fast." When possible, it is better to offer men interventions that produce immediately visible results (Fried 2007). In a general, overcorrection and feminization should be avoided.

It is important to notice that most papers accessing gender dermatological differences did not originate from randomized and controlled clinical trials, and it is difficult to generalize data to general population (Dao and Kazin 2007).

Facial Anatomic Differences Between Genders

Besides clear phenotypic differences between male and female skin determined by hormonal influence such as facial and body hair growth and sebum production in men and fat distribution in women driven by estrogen, there are some specific anatomic distinctions between men's and women's face (Oblong 2012).

Contours of the face accented by strong noses, significant malar–midface configurations, and sharp, well-defined jaw lines have become

hallmarks of contemporary male pattern (Maio and Rzany 2009). In comparison to women, men have increased cranial size, increased skeletal muscle mass, higher density of facial blood vessels, stronger bone structure and less subcutaneous fat, and more-severe facial rhytides (Keaney 2015; Oblong 2012; Keaney and Alster 2013). A study in Japanese men and women documented that men tend to have more-severe wrinkles than women (Tsukahara et al. 2013). The severity of the rhytides must be related to the thinner adipose layer in men regardless of the age (Sjostrom et al. 1972). Men have prominent supraorbital ridges that provide an anatomical landmark for the eyebrow position and have a greater glabellar projection than women.

The brow is higher in the younger woman, but because of the loss of periorbital bone and fat starting in early middle age in women, the brow tends to descend, giving a tired, depressed, or anxious appearance. The brow in men is usually more resistant to downward movement until they are in their 50s (Carruthers and Carruthers 2014).

It is important to notice that women have more prominent upper facial characteristics and men have squarer face and more angled with larger jaws and equally balanced upper and lower facial proportions (Maio and Rzany 2009).

Social and Environmental Aspects

Some factors can accelerate the aging process in men, including cultural aspects (dermatological skincare is considered to be a women habit), emotional and physical stress from work, higher rates of smoking and drinking, and exposure to sunlight without sunscreen use (male skin has a lower minimal erythemal dose threshold than female skin (Broekmans et al. 2003)).

As men have shorter haircut and frequently balding scalps, the sun-exposed skin is prone to actinic keratosis and skin cancer. Men have a globally higher incidence of non-melanoma skin cancer and melanoma when compared to women (Keaney 2015; Rigel 2010). Clark et al. described a probability of developing melanoma in 1.7% in men and 1.2% in women, from birth until death. Men have a twofold higher probability of developing melanoma compared with women between 60 and 79 years of age (Clark et al. 1989).

At the past, research on gender differences of skin biology and its behavior to environmental insults focused on morphology and physiology. New evidence suggests men's skin response to external factors results from unique biological aspects and less usage of sun-protection and skincare products (Oblong 2012). The consequence of those factors is heavily sun-damaged skin and severe rhytides (except in the perioral area). **Adequate sun protection must be strongly recommended in any kind of dermatological approach**.

Men are prone to abnormal healing in the elderly since they have altered inflammatory response and take longer than women to heal acute wounds (Ashcroft et al. 1999).

Aspects of Male Skin

There is a complex interplay between estrogens and androgens in men and women. Sex steroids modulate skin thickness, skin surface pH, wound healing, and potential for infection and diseases (Dao and Kazin 2007). Men's skin is usually thicker and oilier than women's. It has larger pores and generates four times more sebum (Oblong 2012; Kim et al. 2006). Acne can be worse in men due to androgen influences. Sweat output is also higher in men. Some authors found no significant differences between the sexes including lipid compositions and thickness of stratum corneum (Gilliver et al. 2007). Otherwise, there are some relevant peculiarities: dermal compartment is thicker in male skin at all ages. Postmenopausal women experience a decrease in skin thickness, since estrogens play a role in maintaining skin (Bolognia 1995).

Dermatological and Cosmetic Approach in Men

Oily Skin

The skin of male patients is oilier, has larger pores, and usually is an acne-prone skin. The sebum

production is higher. In a daily skin care regimen, oil-control products must be included: keratolytic cleansers, oil-control and dry-touch sunscreens, antioxidants (such as vitamin C, green tea, vitamin E) at the morning, and topical retinoids use at night. Topical retinoids (e.g., tretinoin) and retinoid analogues (e.g., adapalene and tazarotene) help normalize hyperkeratinization and can normalize abnormal growth and differentiation in keratinocytes. Retinoids are comedolytic and reduce microcomedones and also allow enhanced penetration of adjunctive topical compounds (Leyden et al. 2007). Long-term use of topical retinoids is a strategy to obtain a more "youthful" appearance by softening wrinkles, firming the skin, and counteracting photoaging.

Acne in Men

Men's skin usually has larger pores and produces more sebum than women's. Acne can be worse specially on the trunk due to androgens influence.

Acne treatment in men includes cleansers, benzoyl peroxide, salicylic acid, glycolic acid, retinoids, intralesional corticosteroid in inflamed cysts/pustules, oral antibiotics, and oral isotretinoin. Refractory cases can be treated with photodynamic therapy.

As acne can be more inflammatory in male patients and teratogenic effect of isotretinoin is not an issue in this group of patients, oral isotretinoin can be used in order to treat inflammatory acne and acne of the torso and prevent acne scars (Millsop et al. 2013).

Although in women the relationship between acne and insulin resistance is well known, in males this relationship has been poorly investigated. Fabbrocini et al. treated a group of patients with acne and altered metabolic profile with metformin and hypocaloric diet and just followed up another group without any intervention. Their study revealed the importance of diet and insulin resistance in acne pathogenesis and suggested the use of metformin and diet as possible adjuvant therapy for male patients with acne and altered metabolic profile (Fabbrocini et al. 2016).

Based on personal observations of dermatologists, nutritionists, and patients, a problem is an exacerbation of acne in users of whey protein (body builders), which is a protein derived from cow's milk. These observations are in line with biochemical and epidemiological data supporting the effects of milk and dairy products as enhancers of insulin/insulin-like growth factor 1 signaling and acne aggravation (Pontes Tde et al. 2013; Simonart 2012). Prevalence of anabolic androgenic steroids use by competitive athletes and bodybuilders as performance-enhancing drugs is higher in males than women. Many of these steroids are obtained from the internet and dubious sources. Many side effects are noticed: suppression of spermatogenesis, testicular atrophy, infertility, erectile dysfunction, gynecomastia, and acne (Nieschlag and Vorona 2015).

Acne scars can be treated with chemical peelings, dermabrasion, microneedling, and fractional (CO_2, erbium) lasers.

Melasma

Melasma is an acquired hypermelanosis that is more common in women than men. It is important for dermatologists to understand that there are some specific features of melasma in men that seem to differ from women. A survey by Pichardo et al. showed the prevalence of 14.5% among male Latino migrant workers in the United States. The age of onset of melasma in men is 30 years, as in female patients (Sarkar et al. 2003, 2010). It can be a source of embarrassment and social stigma because of its unsightly appearance affecting quality of life (Pichardo et al. 2009). In India, men represent 20–25% of the cases of melasma (Sarkar et al. 2003, 2010).

Sun exposure seems to be the most likely cause in the majority of the cases of men with melasma but genetic predisposition may also play a role (Sarkar et al. 2010). Increased vascularity was found in the lesion of male melasma and also a significant increase of stem cell factor and *c-kit* expression (Jang et al. 2012). Regarding hormonal influences, the circulating LH levels were significantly higher, and testosterone was markedly low in the melasmic men. Sialy et al. concluded that male melasma may involve subtle testicular resistance (Sialy et al. 2000).

In men, the epidermal type and malar pattern of melasma are the most common, but involvement of the neck and forearms has also been reported (Sarkar et al. 2010; Vazquez et al. 1988). Treatment of melasma remains a challenge. Melasma in men should be treated in the same way as in women. Compliance to sunscreen use and topical medications are the mainstay of therapy, and this must be emphasized in male patients. The treatment includes topical medications (antioxidants, lighteners), chemical peels, lasers, and light devices (Q-switched neodymium (yttrium-aluminum-garnet (QS Nd:YAG) laser, Q-switched ruby laser, Q-switched alexandrite laser, copper bromide laser), erbium (YAG laser, 1550-nm erbium-doped fractional laser, and intense pulsed light)). Several peeling agents have been described for melasma treatment, including glycolic acid, salicylic acid, trichloroacetic acid (TCA), retinoic acid, and resorcinol. They improve melasma by removing excess melanin (Gupta et al. 2006).

Hair and Alopecia

Hair contributes significantly to the overall perceived aesthetic of the face. Androgenetic alopecia (AGA) is the most common cause of hair loss in men, and it is usually a concern with considerable psychosocial impact and emotional distress. It involves frontal and temporal scalp areas. The mechanism behind male pattern hair loss is not fully understood. Progressive conversion of terminal hairs into vellus hairs occurs, denudes the scalp, and leads to baldness. This type of hair loss is gradual. Twin studies confirm that hair loss is genetically determined.

Minoxidil topical and finasteride are the approved treatments for male androgenetic alopecia. They prevent hair loss and stimulate partial regrowth of hair. Finasteride, a type II-selective 5alpha-reductase inhibitor, as a causative agent of decreasing dihydrotestosterone (DHT) level, is effective in the treatment of male androgenetic alopecia. An almost 70% reduction in serum and scalp DHT levels can be achieved with 1 mg/day finasteride therapy in men. There are some concerns about side effects or oral finasteride especially decreased libido, gynecomastia, and erectile dysfunction. In 2009, Hajheydari et al. compared the therapeutic effects of 1% finasteride topical gel and 1 mg tablet in treatment of male alopecia. Their study was randomized and double blinded. They found no significant differences between the two groups, and they concluded that the therapeutic effects of both finasteride gel and finasteride tablet were relatively similar to each other (Hajheydari et al. 2009). Recently, a novel finasteride 0.25% topical solution was used b.i.d. for male androgenetic alopecia (Caserini et al. 2014). A strong and similar inhibition of plasma DHT was found with the topical solution and tablet finasteride formulations after 1 week of use (Caserini et al. 2014). In another study, a 3% minoxidil plus 0,1% finasteride lotion was clinical superior to 3% minoxidil in men with AGA (Tanglertsampan 2012). A 5% topical minoxidil solution fortified with 0.1% finasteride can be used to maintain hair growth after initial treatment with 5% topical minoxidil and oral 1 mg finasteride for 2 years, as shown by Chandrashekar et al., thereby obviating the indefinite use of oral finasteride (Chandrashekar et al. 2015).

At past, mesotherapy has received a lot of publicity in the media about its possible role in androgenetic alopecia. This advertised method for the treatment of different types of alopecia is actually lack of data regarding efficacy and possible side effects. The substances injected into the scalp include "cocktails" of plant extracts, homeopathic agents, vitamins, vasodilators, and drugs that may stimulate hair growth, such as finasteride and minoxidil. This subject is controversial and newer forms of *drug-delivery* technique (such as microneedling) are available (Duque-Estrada et al. 2009; Mysore 2010).

Male patients unresponsive to minoxidil can be treated with microneedling. Microneedling works by stimulation of stem cells and inducing activation of growth factors. Dhurat et al. compared 5% minoxidil lotion and weekly microneedling treatment with twice-daily 5% minoxidil lotion. Patients that were treated with combined regimen (minoxidil and microneedling) had a superior clinical response than minoxidil-treated group.

Microneedling was suggested as a promising tool in hair stimulation and also is useful to treat hair loss refractory to minoxidil therapy (Dhurat et al. 2013). Treatment with microneedling showed an accelerated response leading to significant scalp density. There is a boosting effect of microneedling with respect to new hair follicle stimulation in patients with androgenetic alopecia who were poor responders to conventional treatment (Dhurat and Mathapati 2015).

Low-level laser or light (LLL) devices offer alternative AGA treatment options that are not typically associated with adverse side effects or significant costs. There are clinic- and home-based LLL devices. The home-based laser device requires time devoted to carefully moving the comb through the hair to allow laser penetration to the scalp. A novel helmetlike LLL device for hair growth has proven effective in preliminary trials and allows for hand-free use. Regardless, there are few clinical trials that have been conducted regarding LLL devices for AGA and results are mixed. Further research is required to establish the true efficacy of these devices for hair growth in comparison to existing therapies (Gupta et al. 2014)

Data on dutasteride efficacy and safety are limited. Although dutasteride is not currently licensed for treatment of hair loss, randomized, double-blind, placebo-controlled, phase III study with 0.5 mg once daily in male patients with male pattern hair loss showed significant improvement (Eun et al. 2010). Hair transplantation is an option of patient with advanced baldness (Rahnayake and Sinclair 2000).

Pseudofolliculitis of Barbae

Pseudofolliculitis barbae and folliculitis keloidalis nuchae are chronic follicular disorder localized to the beard area and are secondary to the coiled hair shafts repenetrating the skin. These disorders disproportionately affect men of African ancestry, but Caucasians can also be affected. As a matter of fact, pseudofolliculitis barbae can occur in any hair-bearing area where traumatic (shaving, plucking) hair removal occurs (Alexis et al. 2014).

Because this process is induced by shaving its cure is simple: by not shaving or plucking at all and allowing the hairs to grow to beyond 1 cm in length, the disease will spontaneously involute (Lebwoh et al.).

If a clean-shaven appearance is preferred or deemed necessary by occupational or social demands, patients should consider removing the hairs with clean electric hair clippers twice daily or a safety razor once daily at the lowest setting or alternatively depilatory (irritation responds to cortisone creams substituted for aftershave lotions). In the morning before shaving, the beard should be washed with an antibacterial cleanser and hydrated with a moist hot towel followed by applying a cream, gel, or foam lubricant. Taking care to not stretch the skin, a single edged polymer-coated blade can be used to shave along the grain. Shaving is performed in the direction of hair growth, not against it, again to prevent too-close shaving and transfollicular penetration.

Medical therapy of pseudofolliculitis includes retinoids applied at night and low- to mid-potency topical steroids applied in the morning after shaving, the latter replacing commercial aftershave products. Pustular lesions respond topical and oral antibiotics with anti-inflammatory activity. Dark, coarse hairs in both genders can be treated with the long-wavelength 1064-nm Nd:YAG or 810-nm diode lasers. Patients with post-inflammatory hyperpigmentation should use sunscreens and avoid alcohol-based products with burn and sting. Hyperpigmentation is treated with serial chemical peels; tretinoin, azelaic or kojic acid, and 4% hydroquinone (Quarles et al. 2007).

Laser/Light/Radiofrequency/Ultrasound Treatments for Rejuvenation

In general, these procedures can be done with the same parameters as used for women. On the other hand, some lasers and light should be avoided on the beard area to prevent hair damage (see Vol. 3: chapter "► Lasers, Lights, and Related Technologies in Cosmetic Dermatology").

Botulinum Toxin for Cosmetic Use

Aging is a complex process involving two important factors: volume loss throughout the face and repetitive muscle movements that cause wrinkles and folds. Dermal fillers work by providing support for facial structures, whereas botulinum toxin reduces the mimetic effects. In combination, these products can be used effectively to reshape and rejuvenate the face and neck. Dermal fillers can be used to fill the tear trough, fill nasolabial folds and oral commissures, fill the cheeks, raise the cheekbones, reshape the jaw line, and rejuvenate the neck area. This "minimal approach" or "soft lift" (combination of botulinum toxin and fillers) offers a faster, less painful, and less costly alternative to surgical facelifts (de Maio 2004).

Despite the knowledge of differences in facial anatomy between genders, there are few studies that address the distinct aspects of botulinum toxin and dermal fillers. Botulinum toxin is widely used for facial aesthetics, and its use in men continues to increase. The number of men seeking botulinum toxin injections has increased by 8% since 2010 and 268% since 2000 – totaling 363,018 injections in 2011 (Keaney and Alster 2013). Higher doses of onabotulinumtoxinA are used in men than the amount used in women. Some studies found abobotulinumtoxinA to be less effective in men (Keaney and Alster 2013).

In order to achieve a good result with botulinum toxin use in men, it is important to notice the factors shown below:

- Proper dosing.
- Appropriate patient selection.
- Accurate placement of the neurotoxin.
- Maintain the male pattern of the face. The eyebrows must remain in a horizontal and flat shape (and not arched). Male eyebrows are usually flatter and narrower.
- Glabellar projection is greater in men than women.
- Horizontal frontal lines usually appear earlier in male patients.
- The goal is to achieve a more youthful and healthy appearance without being feminine.
- Not overcorrect or overwork (male patients want a natural look).
- The greater vascularity of male skin may contribute to the risk of bruising after botulinum toxin injection ((Fig. 2).

There are two clinical studies with abobotulinumtoxinA use that accounted for gender by adjusting the proper dose or performing subgroup analyses. Brandt et al. showed that women were more likely to respond to the treatment of glabellar lines than men. Treatment of the male glabella required an abobotulinumtoxinA dose greater than 50U (Brandt et al. 2009). Another multicenter, randomized, double-blinded, placebo-controlled study suggested that men are less responsive and have larger muscle mass and more-severe rhytides than women. There were no more adverse events in the men. The investigators recommended using larger doses of abobotulinumtoxinA in men (Baumann et al. 2009).

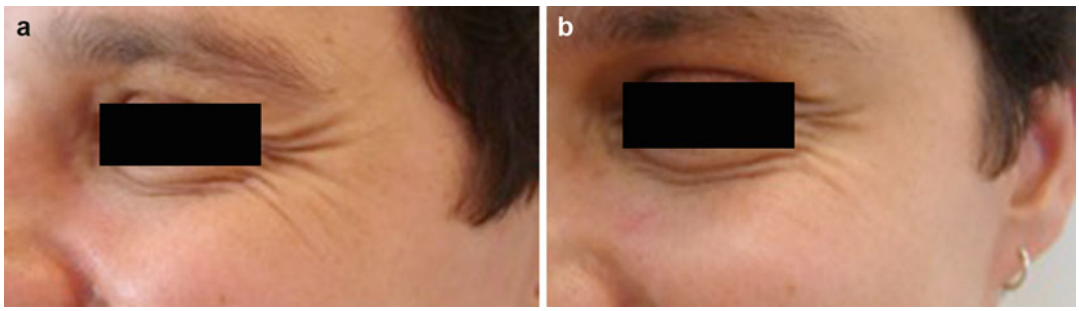

Fig. 2 Treatment of crow's feet with botulinum toxin

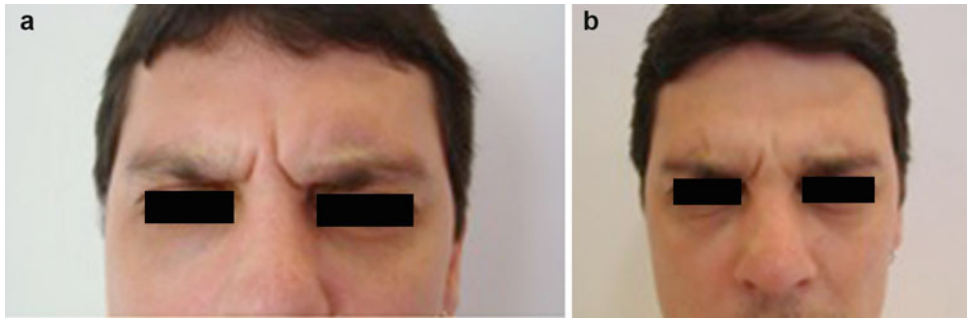

Fig. 3 (**a**) Glabellar lines in men require higher doses of botulinum toxin than in women. This was the first botulinum toxin (35U of onaBT) glabellar treatment of this 33-year-old patient. (**b**) The second figure was the result after 2 weeks, when he needed more sites of injection (including the medial portion of the brow) and a final dose of 55U of onaBT to really achieve a satisfactory result

Carruthers J and Carruthers A have examined the dose–response relationship in men using varying doses of onabotulinumtoxinA and concluded that 20U was an inadequate dose in the glabellar complex and recommended starting men at a dose (40U) approximately twice the typical dose used in women. Not all men require a glabellar dose of 40 U or higher, but most men with hypertrophic and powerful corrugator and procerus muscles certainly do (Carruthers and Carruthers 2005; Jones 2013). See Fig. 3.

In order to avoid a "spock" look or arched eyebrow, which is undesirable in men, lateral fibers of frontal muscle must be treated with botulinum toxin. Small amounts of toxin must be used avoiding lateral brow ptosis.

Benign masseter hypertrophy is a condition that can occur unilaterally or bilaterally. It can be a result from malocclusion, bruxism, clenching, or temporomandibular joint disorders, but the etiology in the majority of cases is unclear. Pain may be a symptom and this dysfunction can be treated with botulinum toxin injections. Aesthetic complain is characteristic of female patients especially Asians, and most treatments published in literature were performed in women (Klein et al. 2014). Excessive facial thinning is not desirable in men. Marked jaws and squared face are male face hallmarks. Unless the masseter hypertrophy is symptomatic or asymmetric or denotes some dysfunction, this particular area is usually not a concern of men.

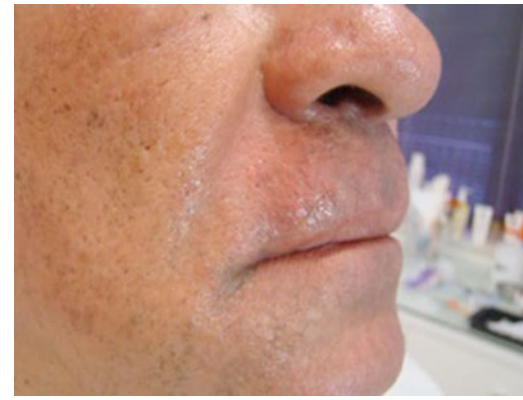

Fig. 4 Dermal fillers can be used to fill nasolabial folds and oral commissure

Dermal Fillers

The anatomic configurations of volume and mass determine the unique pattern of a pleasant male face. The important features to consider are the malar–midface contour, the jaw line, and the nasal frontal projection. The three major landmarks of volume and mass that dominate facial topography are (a) the nose, (b) the zygomatic prominences, and (c) the chin and jawline. Secondary

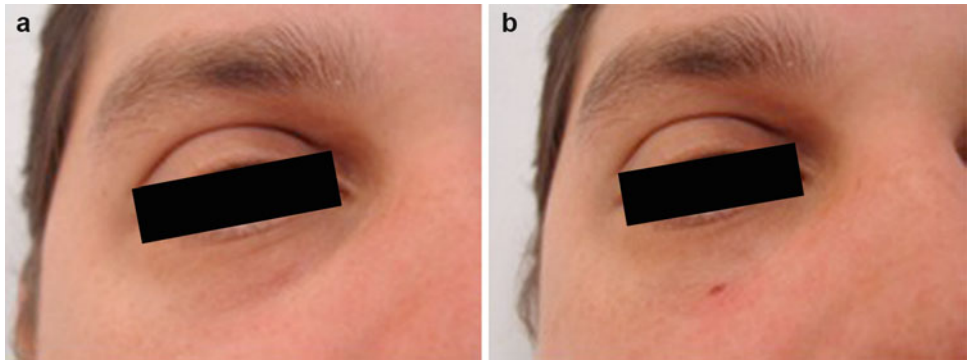

Fig. 5 Hyaluronic acid injection in the tear trough: Pre- and posttreatment

landmarks include the supraorbital ridges, the temporal contours, the premaxilla, and the suborbital region. **Male face is usually squarer and the jaws are stronger**. Mandible projection is more acceptable in males than females (Maio and Rzany 2009). De Maio and Rzany have suggested some guidelines to asses men's face: (a) compare the relative volumes of the face – forehead, middle, and low face of male patients; (b) check the relative proportion of the face before analyzing individual features such as size, shape, texture, and color; and (c) notice the curves and angles typical of a man (Maio and Rzany 2009).

Dermal fillers can be used to fill the tear trough, fill nasolabial folds and oral commissures, fill the cheeks, reshape the jaw line, and rejuvenate the neck area. Denser hyaluronic acid (product destined to restore volume) can be used with microcannula to **reshape the jaw line**.

The presence of darkening in the lower eyelid is common among male adults and can be treated with lasers/light and **injection of fillers in the tear trough**. See Figs. 4, 5, and 6).

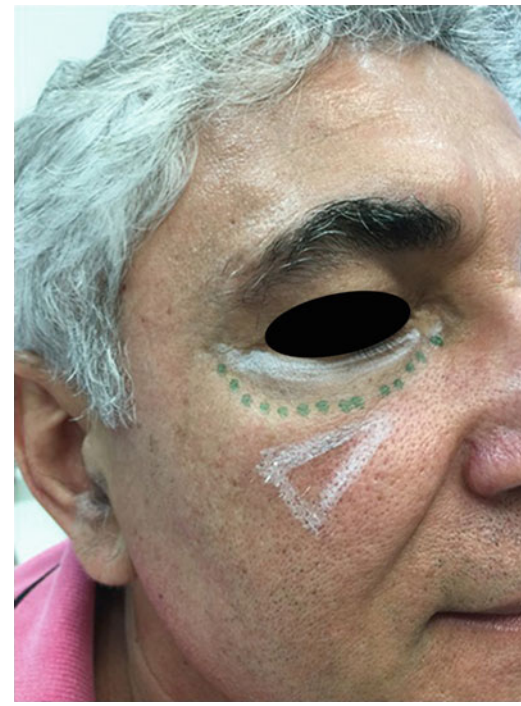

Fig. 6 57 year old man: midface ptosis, laxity of the lid/cheek junction, tear trough deformity. The white triangle shows the shadow zone: mid cheek groove. The white line: palpebral line. The green dot line: palpebromalar groove. Volumizer HA (high cohesive gel) should be used on the malar (triangule) area. Lighter HA product (lower viscosity gel) is the best choice to fill palpebromalar area (submuscular plane and with small amount)

Quality of Life

Gender differences in psychological aspects are influenced by cultural expectations as well as by the surrounding environment. These differences determine patients' responses to their dermatologic and aesthetical conditions as well as the degree to which they may become socially impaired (Gupta and Gupta 1995).

Take-Home Messages

- Strongly recommend sunscreen use, since men are more sensitive to UV radiation and they have a higher risk of skin cancer.
- Establish a daily skincare regimen with oil-free products considering that men's skin is thicker and produces more sebum.
- Be aware of possible influence of diet, vitamin supplements, and hormone use on acne approach.
- Melasma can occur in men and must be treated due to its embarrassment and social stigma.
- Androgenetic alopecia must be treated with oral and topical therapeutic as soon as possible.
- Instruct the patient how to shave properly in order to avoid folliculitis and subsequent hyperpigmentation.
- Considering differences in facial anatomy between genders, botulinum toxin can be used to treat glabellar and frontal lines using higher doses than the ones used in women.
- Avoid arched brows and feminine look by treating lateral fibers of frontal muscle with botulinum toxin.
- Dermal fillers can be used to correct tear trough, fill nasolabial folds and oral commissures, fill the cheeks, reshape the jaw line, and rejuvenate the neck area.

Cross-References

- ▶ Chemical and Physical Sunscreens
- ▶ Cleansers
- ▶ Cosmeceutical Ingredients: Botanical and Non-botanical Sources
- ▶ Hydroxy Acids
- ▶ Nutraceuticals in Dermatology
- ▶ Oral Photoprotection
- ▶ Photoprotection: Concept, Classification, and Mechanism of Action
- ▶ Retinoids
- ▶ Vitamins and Other Antioxidants

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Cosmetic Approach During Pregnancy

Luna Azulay-Abulafia and Eduardo de Oliveira Vieira

Abstract

Pregnancy is a very special moment for every woman, and some physiologic changes occur in her body, including the skin. Skin treatment can be necessary to control some disease that can begin or get worse during pregnancy, and dermatologists must know what can or cannot be prescribed during this period. Clinical and side effects of many different medicaments are well studied and when correctly indicated they can be used. On the other hand, few data about the benefits and the harmfulness of cosmetics and cosmeceuticals is available. This chapter will approach what is known about cosmetics and cosmeceuticals, the indication and the contraindication of these products during pregnancy.

Keywords

Pregnancy • Cosmetic • Cosmeceutical • Skin • Nail • Hair • Fetus • Embryo

Contents

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Introduction

On account of ethical considerations, studies with pregnant women are not possible and studies in animals cannot be extrapolated to humans. The dermatologist must take into account the different phases of pregnancy, and, for sure, the first trimester is the most important for the fetus's development. Pregnancy is divided in number of weeks of gestation better than in trimesters. The probability of damage varies according to the period in weeks to the embryo (fifth to eight week) or to the fetus (from the ninth week). The modifications that occur from the ninth week on are not so important as the ones in the embryo phase (Grunewald and Jank 2015). The fetus is less susceptible to drugs and viruses, but interferences in the normal development of some organs can

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occur. Therefore, every decision for pregnant woman must be weighted: benefit × harm.

For obvious reasons, women want to have a nice appearance at this moment in their lives. Physiologic changes as increased hair growth and darkening of particular areas of the skin (linea nigra, folds, nipple) (Figs. 1, 2, and 3) are some of these undesirable events that the dermatologist is asked about how to deal with.

There are limited data about safety and efficacy of many active products used in cosmetics and cosmeceuticals applied topically during pregnancy. A cosmetic is a product that comprises functions as cleaning, perfuming, protecting, and modifying the external appearance of nails, hair, and skin (including lips and external genitals). The term cosmeceutical is considered an intermediate category between medicaments and cosmetics. These products are not inert to the skin as cosmetics are, as they are able to modify cutaneous structures. Dermatologist should be careful when prescribing cosmeceuticals for a pregnant woman (Kligman 2005a, b; Choi and Berson 2006; http://www.cfsan.fda.gov/~dms/cos-218.html).

Cosmetics

Hair Care

Dyes

The dyes may be temporary (applied during bathing), semipermanent (lasting 4–6 weeks, like henna), and permanent (substances that penetrate the hair, like paraphenylenediamine). There are some considerations in medical literature about Wilms tumor being associated with hair dyes (Duarte et al. 1999; www.americanpregnancy.org/pregnancyhealth/hairtreatments.html). Those findings were not confirmed in natural abortions or fetus malformations in hairdressers, exposed to these products. Some pregnant women use hydrogen peroxide, but due to its rapid metabolization, there is few probability of making any harm to the mother and fetus.

Although there are no adequate studies on that subject, it is advisable to use this kind of products after the first 12 weeks of pregnancy. It is important not to mix different dyes, as the effects on the fetus of the end product are unpredictable (Duarte

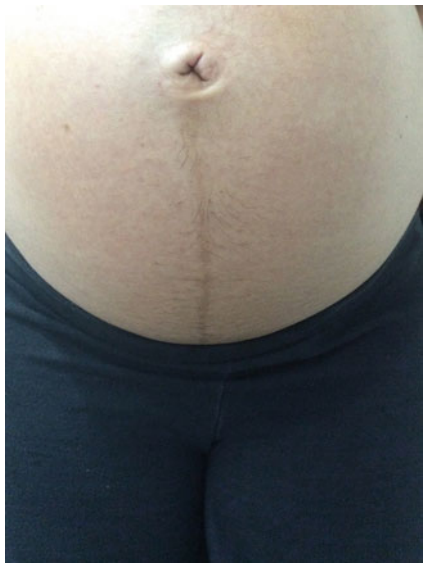

Fig. 1 Linea Nigra

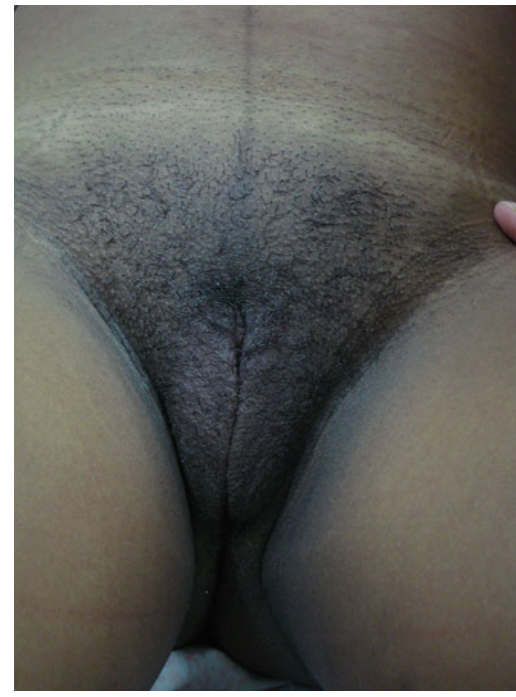

Fig. 2 Darkening of the folds

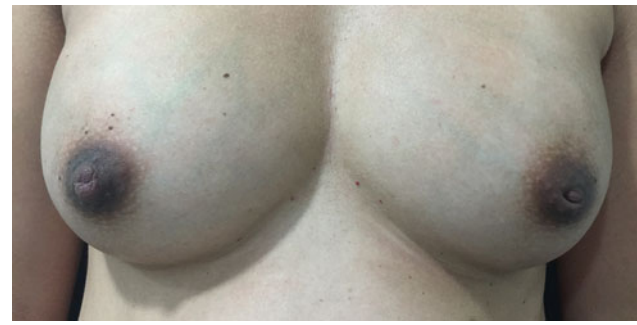

Fig. 3 Darkening of the nipples

et al. 1999; www.americanpregnancy.org/pregnancyhealth/hairtreatments.html).

Straightening and Curling Hair Products

The most common product used for straightening or curling hair is the ammonium thioglycolate that breaks the disulfide bonds in the cortex of the hair shaft. It is described that hairdressers may develop contact eczema when dealing with these substances. One paper (Couto et al. 2013) reported the association of dyes and straightening products with leukemias in children under the age of 2 years old. It is advisable not to use this product in the first 6 months of pregnancy.

Hair Bleaching

Generally, bleaching agents are based on hydrogen peroxide. As already commented before, its metabolization is quick and its use is safe in pregnancy. As a general rule, this kind of products is better used after the second trimester of pregnancy (www.americanpregnancy.org/pregnancyhealth/hairtreatments.html).

Depilatory Products

Calcium thioglycolate is the most common ingredient for depilatory purpose. According to Health Canada guidelines, thioglycolic acid is permitted inside depilatory products at concentrations equal to or less than 5% with a pH of 7–12.7 (Bozzo et al. 2011).

Similarly with other active substances, there are no studies in humans. There is an experimental study in rabbits that showed correlation between thioglycolic acid and low weight fetus without genetic abnormality (Tyl et al. 2003). It is preferred to use after organogenesis is completed (first trimester).

Sodium, calcium, and potassium hydroxide are also found in depilatory creams; they disassociate into sodium, calcium, potassium, and hydroxide ions. These ions are abundant in our body and are part of the diet intake. The systemic absorption of these chemicals is negligible, and their topical use doesn't seem to increase serum levels (www.americanpregnancy.org/pregnancyhealth/hairremoval.html).

Nail Care

Nail Polish and Removers

Dibutyl adipate is used as a plasticizer (materials that soften synthetic polymers by reducing brittleness and cracking) and as solvent in nail polish. It is considered safe in the concentrations commonly used in cosmetics (Andersen 2006).

Phthalates (dibutyl/diethyl phthalate) are included in some nail polish as plasticizers; they are used to decorate and protect the nails. It is advisable to use products phthalate-free, although there isn't any human demonstration of teratogenicity as in animal studies (Levy 2004; Ema et al. 1998).

Ethyl and butyl acetate are solvents used in nail polish; ethyl acetate is also used in nail polish removers. They are considered safe as studies in animal didn't show teratogenic effects (Elder 1989).

Methyl isobutyl ketone used in nail polish removers is considered safe in pregnancy, although there isn't any study in humans. Studies in rat didn't demonstrate embryotoxicity (Johnson 2004).

Ethyl methacrylate used in artificial nails may induce allergic reactions like contact eczema (Andersen 2002).

Self-Tanning Agents

The active ingredient of these products is dihydroxyacetone (DHA); it offers a very little sun protection (perhaps FPS 4). It reacts with amino acids in the stratum corneum and gives a tan color to the skin. It is not a makeup because its effect last for a long period of time and it is not completely washed out with water during bathing. The products in general have 3–5% concentration of DHA. The patient must be informed that it stains clothes, hair, and nails. It is calculated that there is a 0.5% absorption detected in blood. There are no informations about transplacental passage of DHA. So it is better to use it later in pregnancy if strictly desired (Bozzo et al. 2011).

Makeup Products

They are generally safe for use during pregnancy. It is important to avoid products that contain mercury. Also some lipsticks contain lead in its composition and must be avoided too. Inorganic dyes are not systemically absorbed; therefore, they have a safe profile to be used in pregnancy (Duarte et al. 1999; Dickenson et al. 2013).

Cosmeceuticals

Moisturizers

There are different products included in this category with different mechanisms of action to prevent transepidermal water loss (TEWL). A moisturizer can contain occlusive agents, which retard evaporation and water loss; humectant agent, which attracts water from the dermis to the epidermis; and emollient ingredients, which give the smooth and soft texture to the product (Wehr and Krochmal 1987; del Rosso). In general, the use of moisturizers is indicated to prevent the appearance of stretch marks (Fig. 4),

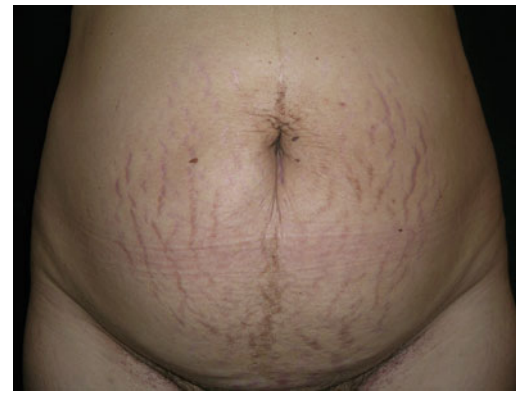

Fig. 4 Stretch marks

but there is no evidence to support this indication. The most frequently used occlusive ingredients are petrolatum, lanolin, mineral oil, carnauba wax, and silicone derivatives. Humectants commonly included in moisturizers formulations are urea, sodium and ammonium lactate, hyaluronic acid, panthenol. Emollient ingredients include dimethicone, cyclomethicone, and ceramides. Formulations must have a balance between these ingredients into different vehicles to be adequate to oily, normal, or dry skins (Simion et al. 2005).

Moisturizers seem safe with no adverse effect on the fetus. There is an exception referring to the use of urea (http://www.anvisa.gov.br/cosmeticos/informa/parecer_ureia_cosmeticos.htm). Brazilian law prohibits its use over 3%, as over this concentration, urea may enhance the absorption of other products topically applied.

Generally, the use of moisturizes in pregnancy intend to prevent stretch marks, but there is no evidence to support that the use of topical moisturizers will do so (Brennan et al. 2012).

Photoprotection

One of the most frequent complains during pregnancy is melasma, the hyperpigmentation that occurs mainly on the face (Fig. 5), which is triggered or aggravated by sun exposure (Purim and Avelar 2012).

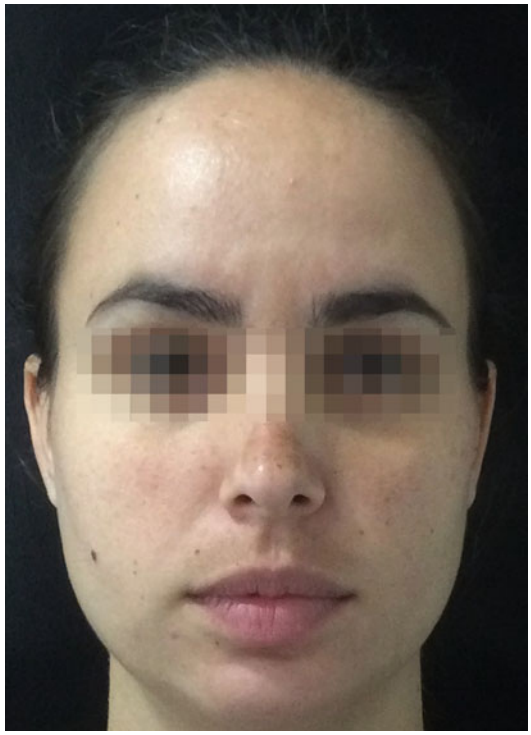

Fig. 5 Melasma

Photoprotection is an important issue to pregnant woman as well as to general population. Photoprotection must consider not only the use of sunscreens but attitudes facing sun exposure, time spent outdoor, less dressing, and the comprehension of the climate changes, partly on account of modifications in the ozone layer. Sunscreens must protect the skin against UVB and UVA radiation, preventing erythema (sunburn), photoaging, and some skin cancers.

Some years ago, physical sunscreens were cosmetically less acceptable as they had a whitish color and a bad spreadability. The new formulas with micronized substances revert these characteristics with a relative downgrade in the sun protection capacity. Physical sunscreens are inorganic or insoluble, based on titanium dioxide and zinc oxide. They reflect UV radiation but also absorb some radiation and release it as heat. The higher absorbance range is for titanium dioxide (250–400 nm). The maximum concentration of these agents approved by FDA is 25% (Kroumpouzos and Draelos 2013).

Chemical sunscreens are organic and soluble. They mainly absorb UV radiation. Salicylates, methoxycinnamate, octocrylene, aminobenzoic acid, and padimate O absorb UVB radiation. Avobenzone absorbs UVB and UVA radiation, but the UVA protection weakens after being exposed to the sun. There are some new trademarks that render stability to the sunscreen like Mexoryl® (ecamsule), Anthelios® (ecamsule, avobenzone, and octocrylene), and Helioplex® (avobenzone and oxybenzone).

There is some discussion about the safety of octocrylene during pregnancy. Odio et al. (1994) in 1994 reported no teratogenicity after oral administration of octocrylene to pregnant rabbits.

Until now, after so many years of use, there isn't any prerogative to justify the fear for not using sunscreens during pregnancy.

Bleaching Agents

One of the most important bleaching agents, used in dermatology, is hydroquinone. Hydroquinone concentration used in cosmetics ranges from 4% to 8%. It was used as a developer in black-and-white photography and in the rubber industry. It is applied to the skin mainly for treating melasma. Hydroquinone penetrates into the epidermis reaching blood levels within the first half hour after application. A study using topical cream with hydroquinone at 100 μg/cm^2 of concentration, on the forehead of man, reported that the urinary excretion was 45.3% of the dose for 24 h after application (Wster et al.).

A study with 99 pregnant women in Africa who used skin lighteners with hydroquinone or with highly potent steroids reported no difference in the outcomes in the hydroquinone group (64 women). However, in the group submitted to the topical use of corticosteroids (28 women), there was a higher rate of low-birth-weight infants (Mahé et al. 2007). In Europe, hydroquinone is forbidden in cosmetics since 2001. For the Food and Drugs Administration (FDA), it is considered category C. On account of insufficient data on the use of hydroquinone, it is advisable not to use in pregnant women to treat melasma or any other condition.

Azelaic acid is used for acne treatment, but can be used as a lightning product as it inhibits tyrosinase, interfering in melanin production. For this purpose, it is an *off-label* indication. It is considered category B for FDA. The absorption of azelaic acid topically applied is approximately 4% for the cream and up to 8% for gel formulation (Akhavan and Bershad 2003). There aren't studies to support its indication during pregnancy, but it can be used if strictly necessary.

Other claimed product for bleaching the skin is kojic acid. It is an antioxidant and it was first isolated from *Aspergillus oryzae* in steamed rice (the term koji means steamed rice in Japanese). It is not approved, by FDA, to be used in over-the-counter products (Nakagawa et al. 1995; Cilliers). Kojic acid is used in different concentrations, ranging from 0.1% to 2% and it should be applied twice a day. A study published in 2010, using kojic acid at 1–4% of concentration, didn't show signs of maternal toxicity or fetal developmental defects. A possible adverse event is contact dermatitis (Burnett et al. 2010).

Topical Hyaluronic Acid

The topical use of hyaluronic acid can be considered safe as it is a natural product in human skin as in the fetus tissues.

Retinoids

Tretinoin

The systemic exposure to retinoids may produce the retinoid embryopathy. Many defects are reported, as micrognathia, anomalies of the ears, facial and palate abnormalities, impairment of the central nervous system, and cardiovascular defects. Despite of the embryopathy described with systemic retinoid, there isn't a study to prove the same alterations after its topical use. A study that compared 215 women, who were exposed to topical tretinoin, with 430 controls could not demonstrate statistical differences in the defects that were found (Jick et al. 1993). The major defects reported were not the same of those described in retinoid embryopathy. Another prospective study with 94 women who were exposed to topical tretinoin in the first trimester of pregnancy reinforces the conclusion of the previous publication in 1993 (Shapiro et al. 1997).

In 2012, a multicentric study in Europe with 235 pregnant women compared women who were exposed to topical retinoids with 444 controls. This publication showed no differences between the groups regarding spontaneous abortion and minor and major birth defects. Retinoid embryopathy could not be identified in any of the children born in the group submitted to topical retinoids (Panchaud et al. 2012).

Another study (Loureiro et al. 2005) compared 389 pregnant women (control group) with a group of pregnant 106 women who used topical tretinoin in the first trimester reported no difference in the outcomes of both groups.

There were few reports of developmental defects on the embryo when the mother was exposed to topical retinoid (Lipson et al. 1993). One case involved a girl who was born with multiple malformations (supraumbilical exomphalos, diaphragmatic hernia, inferior pericardial defect, dextroposition of the heart, right-side upper limb defect) after maternal application of tretinoin cream during the first 5 weeks of pregnancy (Camera and Pregliasco 1992; Navarre-Belhassen et al. 1998). Another case reported is a girl with normal karyotype that was born with coarctation of the aorta, hypoplastic left hand, hypertelorism, and small ear canals. Her mother had used a topical alcohol-based preparation of tretinoin 0.05% and a topical preparation of benzoyl peroxide 2.5% for facial acne before and during 2 months of pregnancy (Camera and Pregliasco 1992; Navarre-Belhassen et al. 1998).

Although the differences reports in literature between women exposed and nonexposed to topical retinoids were not statistically significant, the benefits don't justify its use during pregnancy. As the side effects related to oral retinoids are really very severe, it is not advisable to use retinoids topically in pregnant women.

Retinol

It is considered category C for the FDA. There are evidences that its use can produce clinical modifications in the skin without elevating its levels in the blood. It would be safer than tretinoin; however, it doesn't have enough benefits to justify its use during pregnancy (Leachman and Reed 2006).

Conclusion

The use of topical cosmeceuticals or cosmetics during pregnancy must be based in the medical literature whenever possible. In case of doubt, the best attitude is to avoid the use.

Take-Home Messages

1. On account of ethical considerations, studies with pregnant women are not possible and studies in animals cannot be extrapolated to humans. Therefore, there are limited data about safety and efficacy of many active products used in cosmetics and cosmeceuticals during pregnancy.
2. There are some considerations in medical literature about Wilms tumor being associated with hair dyes.
3. It is advisable not to use straightening and curling hair products in the first 6 months of pregnancy.
4. Hair bleaching with hydrogen peroxide has a quick metabolization and its use is safe in pregnancy.
5. There is an experimental study in rabbits that showed correlation between thioglycolic acid (depilatory creams) and low-weight fetus without genetic abnormality. It is better to use after organogenesis is completed (first trimester).
6. The systemic absorption of sodium, calcium, and potassium hydroxide (depilatory creams) is negligible.
7. Phthalates are included in some nail polish as plasticizers. It is advisable to use products phthalate-free, although there isn't any human demonstration of teratogenicity as in animal studies.
8. Dibutyl adipate is used as a plasticizer and as solvent in nail polish. It is considered safe in the concentrations commonly used in cosmetics.
9. Nail polish and nail polish remover can be used when studies in animals didn't show any teratogenicity. It is advisable to use products phthalate-free.
10. There are no informations about transplacental passage of dihydroxyacetone (self-tanning agent). So it is better to use it later in pregnancy if strictly desired.
11. Makeup products are generally safe for use during pregnancy. It is important to avoid products that contain mercury and lead. Inorganic dyes have a safe profile.
12. The use of moisturizers seems safe with no adverse effect on the fetus. Brazilian law prohibits moisturizers containing urea over 3%.
13. There is no reason to justify the fear for not using sunscreens during pregnancy.
14. Lightening treatment can be done with kojic, but hydroquinone should be avoided.
15. Retinoids should be avoided.

Cross-References

- ▶ Chemical and Physical Sunscreens
- ▶ Cleansers
- ▶ Cosmeceutical Ingredients: Botanical and Non-botanical Sources
- ▶ Hydroxy Acids
- ▶ Oral Photoprotection
- ▶ Photoprotection: Concept, Classification, and Mechanism of Action
- ▶ Retinoids
- ▶ Vitamins and Other Antioxidants

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Cosmetic Approach in Patients with Acne and Rosacea

Daniela Alves Pereira Antelo and Angela Leta da Costa Rocha

Abstract

Acne vulgaris is a chronic inflammatory disorder of the pilosebaceous unit with a multifactorial pathogenesis and a highly variable morphology. Acne is one of the commonest dermatologic disorders encountered in everyday clinical practice with great negative impact on quality of life. Acne affects almost 80% of adolescents and young adults. It affects both sexes and almost all races. Post-inflammatory hyperpigmentation and scarring may occur. Treatment combines topical therapy, oral medication, and/or cosmetic procedures. Superficial chemical peels, phototherapy (blue light and intense pulsed light), and photodynamic therapy can be used as an adjuvant treatment of inflammatory lesions. Acne scars can be reduced by medium and deep peels, dermabrasion, microneedling, and fractional ablative lasers. Rosacea is also a relatively common chronic skin disorder affecting central portion of the face characterized by persistent facial erythema, facial flushing, telangiectasias, and erythematous papules and pustules. It is a chronic dermatosis with recurrent episodes of exacerbation and variable periods of remission. Its exact pathogenesis is still unknown. A variety of both topical and systemic treatment options are available for these patients; however, patient education and routine skin care are also important aspects of treating rosacea.

Keywords

Rosacea • Cosmiatry • Diet • Skin inflammation • Telangiectasias • Pulsed dye laser • Intense pulsed light • Acne, diet, chemical peels, isotretinoin, laser, acne scarring

Contents

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Introduction

Acne vulgaris is a chronic inflammatory disorder of the pilosebaceous unit with a multifactorial pathogenesis and a highly variable morphology. Acne is one of the commonest dermatologic disorders encountered in everyday clinical practice with great impact on quality of life. Acne affects almost 80% of adolescents and young adults (Tanghetti 2013). It affects both sexes and almost all races. Post-inflammatory hyperpigmentation and scarring may occur.

Rosacea is a relatively common chronic skin disorder (prevalence of 10% and predominates in Caucasians) affecting central portion of the face characterized by persistent facial erythema, facial flushing, telangiectasias, and erythematous papules and pustules. Some cases are associated with ocular inflammation and phymatous changes of the nose, forehead, and chin. It is a chronic dermatosis with recurrent episodes of exacerbation and variable periods of remission (Leta 2015; Powell and Raghallaigh 2012). Because rosacea often affects multiple family members, a genetic component is suspected, but the genetic basis of rosacea remains unclear. The diagnosis of rosacea is based on clinical manifestations, but atypical cases may be misdiagnosed. Its exact pathogenesis is still unknown. Dysregulation of the innate immune system and overgrowth of commensal skin organism may have a role in promoting the symptoms (Two et al. 2015a). Rosacea, as a chronic disease, is treatable, but not curable.

Pathogenesis of Acne Vulgaris

Pathogenesis of acne is complex and multifactorial. The pathogenic events occur at the level of the pilosebaceous unit (Das and Reynolds 2014).

Acne was early described in the early nineteenth century, and until the middle of the twentieth century, dermatologists hypothesized that seborrhoea, follicular keratosis, and microorganisms could be individually responsible for acne. Inflammation was only regarded as the final event of the acne process. The importance of these factors has been reevaluated, and recent evidence emphasizes the importance of an inflammatory response (Tilles 2014; Harvey and Huynh 2014).

It is important to analyze carefully all published information due to high and continuous influx of basic and clinical data about acne before drawing any prompt conclusions.

In the etiopathogenesis of acne, there are, conventionally, four central main factors described:

(a) **Increased sebum production**

Increased sebum and alterations of sebum composition are one of the most important etiopathogenic factors in acne. It is directly related to inflammatory process that underlies this disease. There is a confirmed association between sebaceous lipid synthesis and inflammation, particularly peroxidated lipids (Nikiforou et al. 2016). Augmentation of sebum provides an appropriate setting for growth of bacteria and indirectly contributes to the inflammatory phase (Aydemir 2014).

(b) **Abnormal keratinization of the follicular infundibulum (Hypercornification)**

Abnormal hyperproliferation of keratinocytes associated with increased sebum production may result in microcomedo occurrence (Tanghetti 2013).

(c) **Bacterial colonization of the follicle by *P. acnes***

The main microorganism involved in the pathogenesis of acne is *Propionibacterium acnes*. *P. acnes* is a bacterium of the follicle that grows at anaerobic conditions and uses sebum as food (Aydemir 2014). There is some controversy if *P. acnes* is just a member of the normal cutaneous flora or if it is undoubtedly pathogenic. Microbiologists have conducted phylogenetic studies to evaluate profiles of *P. acnes*, and it seems that some *P. acnes* strains may play an etiological role in acne, while others are associated with health (Fitz-Gibbon et al. 2013). It is possible that some strains may be more "inflammatory" than others.

Demodex mites have been shown to be associated not only with rosacea but also acne vulgaris, although it is unclear if their eradication improves the clinical symptoms of the disease. It is important to notice that finding an association between Demodex and acne are not the same as claiming that Demodex plays a causative role (Simpson et al. 2011).

(d) **Inflammation of the follicle and its surroundings**: "**inflammatory response**"

Recent evidence has emphasized the role for inflammation at all stages of acne lesion development, perhaps subclinically even before comedo formation (Rocha et al. 2014).

This is different from the past and conventional theory that acne results from colonization of *P. acnes* in the duct of the sebaceous follicle that causes the immune response which turns the comedo to an inflammatory acne lesion. Some papers support that acne is primarily an inflammatory disease (Tanghetti 2013). Various immunologic events are described during inflammation in acne lesions (and even in unaffected skin) such as upregulation of inflammatory mediators, elevation of $CD3^+$ and $CD4^+$ T cells, expression of pro-inflammatory peptidases on sebocytes, and activation of inflammatory cytokines by *P. acnes* (Tanghetti et al. 2014).

A key response is the recruitment of activated Th1 lymphocytes leading to early acne lesions. Recent findings on T helper 17 cell involvement in acne were described. Th17 cells are also potent inducers of tissue inflammation and may play a role in acne pathogenesis, but further studies are necessary (Kim et al. 2002).

Besides the described aspects, research about influence of diet and nutrition, genetic and oxidative stress in acne development are being conducted but without unequivocal influence until present (Nikiforou et al. 2016).

Classification of Acne Vulgaris

Even though there is no consensus on a single or a better way to classify acne, it is of utmost importance that dermatologists be aware of the various classification systems, since they guide both therapeutic decisions and interpretations of literature. The classification can be based on the overall assessment of the number, type, and complications of injuries. Another possible clinical classification system is based on the prevalent morphology of the cutaneous injuries: comedonian/noninflammatory, with open and closed comedones (see Fig. 1); inflammatory, with erythematous papules, pustules, and nodules (see Fig. 2) and nodular pseudocysts; or mixed ones, in which all types of injuries are present (see Fig. 3). The classification system based on the acne level of severity can be clinically categorized as mild, moderate, or severe, depending on the number and type of skin injuries, as well as the extent of the involved area. Although there are several classification systems that define acne severity, there is no established standardization, and its interpretation is often subjective (Eichenfield et al. 2013; Strauss et al. 2007).

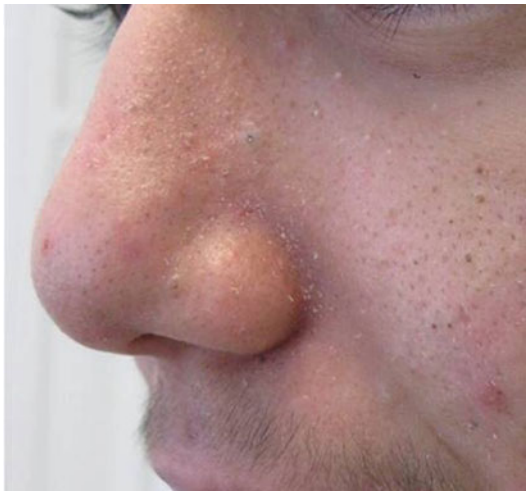

Fig. 1 Comedonian/noninflammatory acne, with open and closed comedones

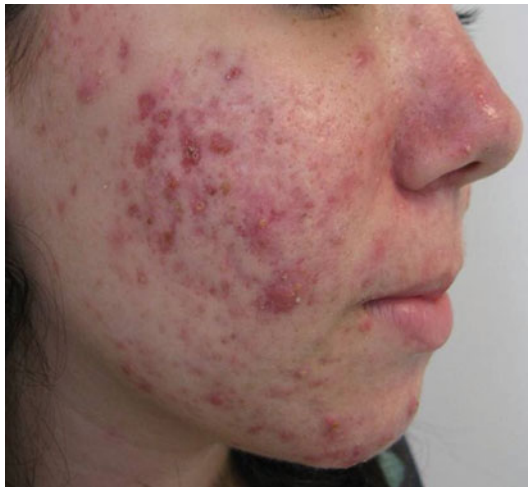

Fig. 2 Inflammatory Acne, with erythematous papules, pustules, and nodules

Special Topic: Adult Female Acne

In some cases, acne can persist up to adulthood or even begin in adult life, especially in female patients (Ramos-e-Silva et al. 2015). Acne no longer can be considered as a disease characteristic of adolescence (Dreno 2015). In recent years, the incidence has increased in female adults (Rocha et al. 2014; Albuquerque et al. 2014). The reason for this increase remains unclear.

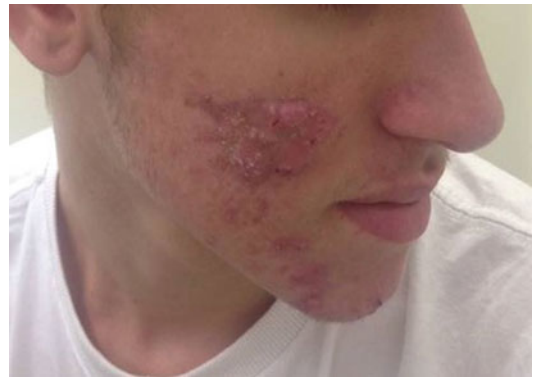

Fig. 3 Inflammatory acne in which all types of injuries are present

Acne can be triggered or worsened by exogenous factors, and modern life presents many stresses including urban noises, socioeconomic pressures, and light stimuli. Women are especially affected by stress during daily routine combining job in the labor market and the duties of a mother and wife. Sleep restriction with its several negative consequences on health may affect hormonal secretion and the immune system. It is reasonable to suppose that is a connection between stress, sleep deprivation, and adult female acne (Albuquerque et al. 2014).

Based on time of onset, two subtypes of adult female acne are recognized: "persistent acne" which is continuous from adolescence (80% of cases), while "late-onset acne" (20% of cases) first presents in adulthood (Dreno et al. 2013; Holzmann and Shakery 2014).

It causes a negative physiological impact particularly in women who have not had acne at puberty.

The clinical aspects of adult female acne are often distinct from adolescent acne. In adults, inflammatory lesions (particularly papules, pustules, and nodules) are generally more prominent on the lower chin, jawline, and neck, and comedones are more often closed comedones. Adult acne is mainly mild-to-moderate and may be refractory to treatment (Dreno et al. 2013).

Genetic and hormonal factors are thought to play key roles in pathogenesis of adult female acne (Dreno 2015). Acne may represent many

systemic diseases or syndromes, such as congenital adrenal hyperplasia, seborrhea-acne-hirsutism-androgenetic alopecia syndrome, polycystic ovarian syndrome, and hyperandrogenism-insulin resistance-acanthosis nigricans syndrome (Zouboulis 2014). Recently, researchers have found increase in total cholesterol levels and low HDL-cholesterol in adult female patients with grades II and III of acne (papule-pustule acne). It is important to diagnose dyslipidemia early in those patients in order to prevent metabolic syndrome (da Cunha et al. 2015).

We must pay attention that acne can result from polycystic ovary syndrome (PCOS), a heterogeneous condition characterized by androgen excess, ovulatory dysfunction, and polycystic ovaries. It affects between 6% and 8% of women and is the most common cause of infertility. Insulin resistance is almost always present, regardless of weight, and they often develop diabetes and metabolic syndrome. PCOS criteria require that patients have at least two of the following conditions: hyperandrogenism, ovulatory dysfunction, and polycystic ovaries. Weight loss through dietary modifications and exercise is recommended for patients with PCOS who are overweight (Mortada and Williams 2015).

Effect of androgenic hormones may influence adult female acne occurrence. Sebum production is stimulated by androgens. Requesting sexual hormones serum levels may be interesting especially in acne female patients with irregular menses, hirsutism, and worsening of acne at premenstrual phase. Increased serum androgens levels correlate with the presence of severe nodular acne, but alterations in hormone profile may not be found but in some cases (particularly in mild to moderate acne). An increased receptor sensitivity to androgens may be present or there is high local production of androgens within sebaceous gland that leads to increased sebum production (Aydemir 2014; Khondker and Khan 2014).

The approach of adult female acne must combine standard treatments with adjunctive cosmetic therapy (Dreno et al. 2013). Retinoid/antimicrobial combinations may be of interest for the treatment of adult female acne given the chronic course of the disease, the high likelihood of the presence of antibiotic-resistant *P. acnes*, and the poor adherence of patients to other long-term therapies. Fifteen percent azelaic acid gel or 0.1% adapalene gel can be prescribed (Thielitz et al. 2015). Oral hormonal treatment or isotretinoin may be required in patients with severe acne or disease that is refractory to other treatments. Combined oral contraceptives may be beneficial in inflammatory and noninflammatory adult female acne (Dreno 2015).

Special Topic: Diet and Acne

Although the effect of food and acne has been discussed intensively, definite evidence about this could not be demonstrated. First diet intervention in order to treat acne was made in 1967 (Hagerman 1967).

Although the beliefs of patients in this direction are very strong, scientific bases are very weak, and the place of prescribing a diet is controversial (Aydemir 2014). Fried food, cola, dried fruits, and fatty foods were the main culprits at past.

There has been an influx of studies examining the link between diet and acne over the past decade. Some evidence has emerged suggesting a possible link between dairy products and acne, which warrants further research (Simpson et al. 2011).

New articles have recently brought to light evidence contrary to previous findings. Some researchers believe that prevalence of adult acne in the USA appears to be increasing over the last few decades. Since significant changes in germline genetic variants are unlikely to have occurred over the last years, they suggest that environmental variables, including diet, may have a role. They have suggested a link between refined carbohydrates and acne. Based on their data, dermatologists should encourage their acne patients to minimize their intake of high glycemic index foods (Mahmood and Bowe 2014).

Concerning metabolic aspects, fasting insulin levels were higher in patients with severe acne than controls. Insulin resistance may have a role in the occurrence of acne, and a low-glycemic diet may be theoretically beneficial in these patients, but this must be confirmed (Emiroglu et al. 2015).

Hyperinsulinism, through an increase in androgen levels, stimulates sebum production, which plays a fundamental role in the development of acne. Extreme calorie restriction drastically reduces the level of sebum excretion. This can be reverted with the adoption of a normal diet (Ludwig 2002).

The relationship between acne and insulin resistance was shown not only in women but also in males. Metformin plus hypocaloric diet for 6 months resulted in improvement of acne in male patients with altered metabolic profile suggesting the influence of diet and insulin resistance (Fabbrocini et al. 2015). Insulin growth factor-1 (IGF-1) may influence acne pathogenesis through its role in keratinocyte proliferation, sebaceous lipogenesis, and androgen synthesis. The significant association between high expression of IGF-1, high body mass index (BMI), and severe acne underlies the value of dietary intervention (Seleit et al. 2014).

Some studies have suggested an association between the ingestion of milk derivatives and acne in spite of them having a low glycemic index. That is because they paradoxically increase the levels of IGF-1, leading to the development or aggravation of acne. This can be more severe when fat-free milk is ingested, showing that this association is not due to the fat content of milk, which strengthens the theory of IGF-1 levels (Adebamowo et al. 2005, 2006).

Chocolate has always been liked to acne as a common popular sense. As a matter of fact, many patients complain about the development of new acne lesions after ingesting chocolate. Commercial chocolate bars, especially with high milk content, have a great amount of carbohydrates which increase the postprandial plasmatic levels of IGF having an insulinotropic profile. This is worth considering if you have been convinced of the comedogenic effect of a high glycemic index diet (Costa et al. 2010).

It is known that iodine ingestion can exacerbate acne. The iodine found in milk due to supplementation of the diet offered to animals can be linked to acne (Grace and Waghorn 2005).

It is important to exclude from diet supplementations linked to acne such as whey protein used by bodybuilders. Whey protein supplementation precipitated acne flare in teenagers. Whey protein may be the fraction of dairy products that promote acne formation (Silverberg 2012).

A diet rich in zinc and vitamin A may be beneficial in acne patients. An aspect that supports this association is the fact that a low-zinc diet worsens or activates acne (Costa et al. 2010).

More scientific studies with interventionist, randomized, controlled, and double-blinded design are needed to evaluate the impact of nutritional factor on acne occurrence.

Treatment of Acne Vulgaris

Acne vulgaris starts at puberty and usually persists for several years, causing negative impact on mood, self-esteem, and other quality-of-life parameters, regardless of the disease severity. Acne pathogenesis is complex and multifactorial. One must act on the multiple factors involved in order to achieve therapeutic results. There is a variety of available medical therapies available, either systemic or topical, which can be chosen based on the severity of this illness and adjusted according to clinical response and disease progression. The guidance for patients about the predisposing factors, the pathology chronicity, and the expectations for immediate results must be clear and, thus, seek to motivate them to have a better treatment adherence. Self-inflicted injuries can lead to exacerbation of acne, dyschromias, and even scar formation.

Topical Therapy

One of the main constraints of topical therapy, especially when used on the face, is the high adverse reaction frequency, with signs and symptoms of skin irritation. This comes from the active ingredient itself and/or from the characteristics of the employed vehicle. In addition, many products sold without medical prescription (OTC) may cause skin abrasion and irritation, reducing the tolerability at the time of application of specific medications. Many patients may discontinue treatment or do it inadequately due to these

adverse effects. Noncomedogenic and oil-free moisturizers and smoothing cleaning agents are often necessary to avoid or minimize skin dryness, redness, and scaling, which may be caused by the therapeutics (Del Rosso and Brandt 2013; Thiboutot and Del Rosso 2013; Feldman and Chen 2011)

Topical Retinoids

There is a consensus that topical retinoids, alone or in combination, are the first therapeutic approach for mild to moderate acne and their effectiveness is well documented. In general, these substances control microcomedone development, reduce the existing inflammatory injuries, and reduce new injury development. They act by regulating the follicular keratinocytes (reducing scaling of the epithelium of the follicles) and modulating the immune response (producing anti-inflammatory effect). In addition of having direct effect on keratinocytes, these drugs act most likely enhancing other topical medications penetration, including benzoyl peroxide (BP) and antibiotics. Topical retinoids such as tretinoin and adapalene reduce the free fatty acids produced by the metabolism of Propionibacterium acnes (*P. acnes*) lipase in microcomedo (Gollnick et al. 2003; Montagner and Costa 2010).

Tretinoin, isotretinoin, adapalene, and tazarotene are the most commonly used retinoids and are available in a variety of formulations and concentrations. Some studies carried out to try to assess the superiority between these substances showed that all these drugs are effective when used properly. Patients should be advised that retinoids can cause irritation, erythema, scaling, dryness, itching, and burning sensation. In order to reduce these side effects, one must temporarily reduce the frequency and timing of applications and start formulations of less irritative vehicles and lower concentrations. Tretinoin should be used at night at concentrations ranging from 0.01% to 0.1% depending on the severity. We recommend the use of an oil-free sunscreen, since this medication offers sensitivity to ultraviolet radiation. If you need to use tretinoin and BP concomitantly, tretinoin should be applied at night and BP during the day as it can inactivate retinoid if used together. Isotretinoin at the concentration of 0.05%, is less irritative when compared to tretinoin and does not provoke photosensitivity. Topical isotretinoin is not currently available in the USA. Adapalene is less irritative, is more stable, and is not inactivated by solar radiation. It is sold in 0.1% and 0.3% concentrations and can be safely combined with benzoyl peroxide (BP) and topical antibiotics (Leyden and Grove 2001; Leyden 2003; Hsu et al. 2011; Dunlap et al. 1998). Tazarotene (0.05% and 0.1%) is an effective topical retinoid, but it is used less often as a first-line agent in the treatment of acne, as it is known to be more irritative (Bershad et al. 2002). Topical retinoids should also be used in the maintenance treatment to prevent recurrences. Tretinoin, isotretinoin, and adapalene are classified in category C (fetal risks cannot be ruled out), and therefore their use is avoided during pregnancy. Tazarotene is classified in category X (contraindicated during pregnancy) (Murase et al. 2014).

Antimicrobial Agents

Topical antibiotics have been used for several decades for acne control. Clindamycin (1%) and erythromycin (2–4%) are available in various topical formulations and have proven efficacy. They reduce inflammatory mediators and *P. acnes* amount in the pilosebaceous units, making them useful in the treatment of mild to moderate inflammatory acne. However, evidence has shown that due to the emergence of less sensitive strains of *P. acnes* and the risk for bacterial resistance induction, these oral antibiotics should not be used as monotherapy (Gollnick and Schramm 1998; Toyoda and Morohashi 1998). Clindamycin and erythromycin are classified as category B by FDA (there is no evidence of human fetal risk even though there are possible risks in animals) (Murase et al. 2014).

Benzoyl peroxide (BP) is a bactericidal agent, available in varying concentrations (2–10%) and in

many presentations (liquid or bar soap, lotion, gel, and cream). It is found in a variety of products without medical prescription (OTC), and its effect and irritative discomfort depend on its dosage. Patients should be advised that this medication can cause hair and clothes discoloration. It is classified as category C by FDA. BP is one of the most potent drugs in reducing the count of *P. acnes* but also presents comedolytic properties, probably by reducing free fatty acid formation, increasing follicular flaking, and decreasing follicular plugging formation. It is capable to prevent and eliminate the development of *P. acnes* resistance. Some studies have shown that no topical antibiotic was more effective than BP when used alone (Eichenfield et al. 2013; Gollnick et al. 2003).

Azelaic acid in gel and cream presentation, 15% and 20%, respectively, may be beneficial in mild comedogenic and inflammatory acne. This substance acts on abnormal keratinization, inhibits *P. acnes* proliferation, and exerts depigmentant action. It is generally well tolerated and may cause mild adverse reactions. Due to these characteristics, it is considered to be a good option for patients who do not tolerate retinoids or as a supporting therapy for post-inflammatory hyperpigmentation (Leeming et al. 1986; Graupe et al. 1996; Cunliffe and Holland 1989). Azelaic acid is classified as category B by FDA (Murase et al. 2014).

Dapsone 5% gel has known antimicrobial and anti-inflammatory effects. However, its activity in the treatment of acne does not appear to be correlated to inhibition of *P. acnes*. Studies showed statistically significant reduction of inflammatory and noninflammatory injuries when compared to the vehicle (Draelos et al. 2007; Lucky et al. 2007). Another trial found that topical dapsone is safe and effective in the controlling inflammatory injuries when used with vehicle or associated with topical retinoids and BP (Fleischer et al. 2010). This gel applied twice a day proved to be safe, even in patients with glucose 6 phosphate dehydrogenase (G6PD) deficiency and those who are allergic to sulfonamides (Webster 2010; Del Rosso 2007). Erythema and dry skin effects are common adverse effects. Temporary orange skin pigmentation may occur when BP and topical dapsone are used concomitantly. Dapsone is classified as category C by FDA (Murase et al. 2014).

Salicylic acid is another antimicrobial substance found in many formulations without medical prescription. Primarily, it is a moderate comedolytic and may be useful in mild comedogenic acne. It is far less effective than topical retinoids, but also better tolerated.

Therapeutic Combinations

Currently, combination therapies are the best way to control acne vulgaris, particularly, when therapeutic agents with complementary mechanisms of action are used. Associations between BP-clindamycin, BP-erythromycin, retinoid-BP, and retinoid-clindamycin target multiple etiopathogenic factors in almost every grade and intensity of acne vulgaris, treating non-inflammatory and inflammatory injuries concomitantly. Therapeutic results achieved by these combinations are superior when compared to their components separately used.

One advantage observed when topical antibiotic is associated with BP or retinoid is that this combination enhances antibiotic therapy clinical efficacy and minimizes bacterial resistance, which can occur when there is prolonged exposure to topical and/or systemic antibiotic.

The association of adapalene with BP has shown superior results when compared to monotherapy or single vehicle due to synergism between anti-inflammatory and bactericidal action of its components, respectively. BP penetration is enhanced in this association and features lower risk of cutaneous irritation in daily use, since the substances are combined in effective lower concentrations.

New expectations concerning triple combination therapy have emerged. Clinical reports point to the possible benefit of adapalene/tretinoin associated with BPO and clindamycin. These associations are level III evidence and await further studies until their use becomes safer (Eichenfield et al. 2013; Gollnick et al. 2003; Toyoda and Morohashi 1998; Thiboutot et al. 2009).

Mild		Moderate		Severe	
	Comedonian	Papular/ pustular	Papular/ pustular	Nodular	Nodular/conglobata
Option 1	Topical retinoids	Topical retinoids +topic antimicrobial	Oral antibiotic + topical retinoid+/− BP	Oral antibiotic + topical retinoid +/− BP	Oral isotretinoin
Alternatives	Retinoid (other) or salicylic acid	Topical retinoid (other) + topic antimicrobial drug oral	Oral antibiotic (other) + topical retinoid (other) +/− BP	Oral Isotretinoína or oral antibiotic (other) +topical retinóid +/− BP	High- dose oral Antibiotic + topical retinoid + BP
Alternatives for women	Option n° 1	Option n° 1	Oral antiandrogens + topical retinoid +/− topic antimicrobial	Oral antiandrogens + topical retinoid +/− oral antibiotic +/− antimicrobial (other)	High dose oral antiandrogens + topical retinoid +/− oral antibioticl +/− topic antimicrobial (other)
Pregnancy	Physical removal of comedone Ázelaic acid		Physical removal Topical erythromycin Azitromycin/ oral erythromycin		
Maintenance	Topical retinoids		Topical retinoids + BP		

Modified table from Gollnick et al. (2003).
BP benzoyl peroxide.

Acne Treatment Algorithm

Systemic Therapy

Systemic therapy is justified for patients with nodular acne or inflammatory acne that does not respond to topical therapy alone. The agents employed in systemic therapy include antibiotics, isotretinoin, and hormonal agents.

Oral Antibiotics

They have been used for several decades in the control of moderate to severe acne and act directly on reducing the population of *P. acnes*. In addition, there is evidence supporting their effectiveness for anti-inflammatory activity (change the neutrophil chemotaxis, macrophage functions, and cytokine production). Oral antibiotics are usually well tolerated. In 2003 and 2009, recommendations were adopted by an international group of experts that make up the Global Alliance to Improve Outcomes in Acne (GAIOA) regarding the use of oral antibiotics in acne therapy (Gollnick et al. 2003; Thiboutot et al. 2009).

The Guidelines of 2009 suggest that these antibiotic therapies should be administered for 3 months and then discontinued if the patient has little or no response. Other guidelines developed by medical organizations or based on government agencies recommend treatments limited to a 3–6 months period (Thiboutot et al. 2009; Katsambas and Dessinioti 2008). Long-term courses or over 6 months are not recommended. The major concern related to the use of oral antibiotics in acne therapy is the increasing bacterial resistance. Therefore, monotherapy and concurrent use of oral and topical antibiotic without BP

must be avoided, especially if they are chemically different. Most commonly used oral antibiotics are tetracyclines (tetracycline, minocycline, doxycycline, lymecycline), macrolides (erythromycin and azithromycin), and sulfamethoxazole-trimethoprim. Even though first-generation tetracyclines and erythromycin continue to be used, the therapeutic response to these agents has declined, probably due to the greater prevalence of drug-resistant strains of *P. acnes*. In women, vaginal candidiasis can be observed in the course of all oral antibiotics used to treat acne. The macrolides and tetracyclines can lead to gastrointestinal intolerance (Montagner and Costa 2010; Katsambas and Dessinioti 2008; Leyden and Del Rosso 2011; Lee et al. 2014; Chelsey et al. 2015; Del Rosso and Kim 2009).

Several pharmacokinetic factors can influence acne vulgaris antibiotic therapy results: drug solubility, gastrointestinal permeability, systemic absorption, tissue distribution, and target tissue uptake. Thus, drugs with greater solubility and permeability are better absorbed and distributed, and those that are more lipophilic penetrate better in the follicular tissue which is rich in lipids and where the therapeutic target, *P. acnes*, is found. Second-generation tetracyclines, minocycline, doxycycline, and lymecycline induce a faster response than the first generation (tetracyclines), since they present characteristics that favor their absorption and suffer less interference with fatty food intake or minerals, such as iron and calcium. As minocycline is the most lipophilic, it has greater permeability than doxycycline and therefore, faster absorption and diffusion in tissues, being able even to cross the brain/blood barrier. These differences in pharmacokinetics influence their efficacy and tolerability. Studies have shown that minocycline seems to be more effective, despite being associated with more adverse effects (Leyden and Del Rosso 2011). Lymecycline demonstrated efficacy comparable to minocycline and a better safety profile (Katsambas and Dessinioti 2008).

Doxycycline may be associated with photosensitivity, especially with doses higher than 100 mg/day, and with esophagitis. Minocycline is not associated with phototoxicity, but it may induce pigment deposit in the skin, mucous membranes, and teeth, especially when used for long periods and at high dosages. There have also been cases of autoimmune hepatitis, drug-induced lupus erythematosus, hypersensitivity syndrome, and vestibular alterations associated with its use (Leyden and Del Rosso 2011).

Azithromycin is effective in the treatment of inflammatory and noninflammatory injuries with results comparable to tetracycline, minocycline, and doxycycline. It can be used safely during pregnancy, and its major side effects are related to gastrointestinal disorders. Due to their pharmacokinetic characteristics with a long half-life, several therapeutic schemes are proposed. Trials with azithromycin administered at a dose of 500 mg/day during 4 days showed comparable efficacy to minocycline. It demonstrated good tolerability, effectiveness, and patient compliance to treatment in the form of pulse therapy (500 mg/day for 3 days in a row and repeated at intervals of 7 days, for 3 cycles). However, due to high incidence of resistance to other bacterial agents in the population, further studies should be carried out, and this should not be a first-choice option (Montagner and Costa 2010; Katsambas and Dessinioti 2008).

For children under 8 years of age, pregnant women, and those allergic to tetracyclines, alternative antibiotics are erythromycin, azithromycin, and sulfamethoxazole-trimethoprim (SMZTMP). SMZTMP is usually avoided due to the adverse effects related to farmacodermia and hematological disorders (Leyden and Del Rosso 2011).

According to FDA classification, tetracyclines are classified as category D (positive evidence of risk to the fetus from clinical data), erythromycin (non-estolate) and azithromycin as B, and sulfamethoxazole-trimethoprim as C (Murase et al. 2014).

Hormone Therapy

Hormone therapy is indicated as a second choice treatment for women with moderate to severe acne and is resistant to first-line treatments or those that present other androgenic features. The concomitant use of conventional topical therapies and systemic antibiotics may be recommended.

Combined oral contraceptives contain estrogen and progesterone. Estrogens (ethinyl estradiol) present in these medications may be beneficial for patients with acne; however, progestins can exacerbate this condition. The most recent, third-generation contraceptives (desogestrel, norgestimate, and gestodene) contain less androgenic activity and, therefore, are theoretically less likely to exacerbate acne. The mechanism of action of oral contraceptives is related to inhibition of gonadotropins, ovarian or adrenal androgen, in addition to stimulating hormone-binding globulin (SHBG) synthesis which, in turn, reduces free testosterone plasma concentration (Montagner and Costa 2010). It has been shown that combination of ethinyl estradiol and norgestimate is beneficial for the treatment of acne vulgaris (Lucky et al. 1997). Graduated doses of ethinyl estradiol, combined with stable doses of norethindrone acetate, have an already proven minimal androgenic activity and it is also a therapeutic option (Boyd et al. 2001). Drospirenone is another progestin approved by the FDA for moderate acne and associated with ethinyl estradiol presented fewer adverse effects (Thorneycroft et al. 2004). There is no consensus yet about what would be the best combination.

Before prescribing oral contraceptives for acne treatment, it is essential to identify risk factors and contraindications such as genetic coagulation disorder, prolonged immobilization and/or thromboembolism history, heart disease, hypertension, obesity, smoking in women over 35 years, diabetes mellitus, liver disease, headache and migraine, history of breast, endometrium, and liver cancer. There has been a lot of discussion about the risk of venous thromboembolism and a consensus that risk is low when well-indicated and appropriate control measures are applied. Combining oral antibiotics is still a challenge, since there is risk of reducing the contraceptive effectiveness due to intestinal flora changes and consequent reduction of estrogen intestinal absorption. However, there is evidence showing that estrogen blood levels remain normal in the presence of doxycycline and tetracycline.

The clinical improvement is achieved within 6–9 months continuous use (Montagner and Costa 2010; Bettoli et al. 2015). These agents are ideal for women seeking birth control methods and for those who are not candidates or are unresponsive to oral antibiotics or isotretinoin. Oral contraceptives can be particularly useful for women with polycystic ovarian syndrome. The action of other contraceptives containing estrogens, such as transdermal patches and vaginal rings, has not yet been studied in the treatment of acne (Strauss et al. 2007).

Spironolactone is a potassium-sparing diuretic, which displays a moderate peripheral antiandrogenic activity. It is classified as category D by FDA. This drug is usually quite effective in treating women with persisting acne or in those cases arising after adolescence. The administration of spironolactone is initiated with a 50 mg/day dose, and it can be increased up to 200 mg/day, as needed. However, the vast majority of patients respond favorably to a 100 mg/day dosage. Although monitoring serum potassium is unnecessary, whenever it is used in high doses or in patients with cardiac or renal impairment, the risk for hyperkalemia should be considered.

Menstrual irregularities and painful gynecomastia may be associated with this drug, particularly with higher doses (>100 mg/day). These adverse effects do not occur when spironolactone is combined with an oral contraceptive containing estrogen. This combined therapy also seems to increase the therapeutic benefits achieved by young people with acne vulgaris in post-adolescence.

Spironolactone should not be administered together with lithium carbonate due to its potential to increase lithium serum levels and, as a consequence, increase toxicity (Shaw 2000).

Cyproterone acetate, a derivative of 17-alpha-hidroxiprogesterona, inhibits central secretion of gonadotropin and reduces 5-alpha reductase activity in the peripheral receptor. When it is administered separately, its dose may range from 25 to 50 mg/day. Higher doses are more effective in hirsutism control (Montagner and Costa 2010; Bettoli et al. 2015). The most widely used commercial association is 17-alpha-hidroxiprogesterona along with ethinyl estradiol.

Low-dose corticosteroids are indicated in patients with congenital adrenal hyperplasia, since they suppress the production of androgens by the adrenal gland. In cases of severe inflammatory nodular acne, they are indicated for a short period in higher doses.

Flutamide, a nonsteroidal antiandrogen indicated for prostate cancer and hirsutism treatment, is effective in acne control, but its use is limited due to liver failure risk. We have previously used oral flutamide with great decrease of the oiliness of the skin, but we have abandoned its use due to liver damage cases.

Metformin is not strictly classified as a hormone therapy for acne, but it can be useful in some cases of hyperinsulinemia with or without associated overweight.

Isotretinoin

Isotretinoin (13-cis-retinoic acid) is a retinol derivate and a main systemic drug for acne vulgaris. It is indicated for patients with severe nodular acne and those refractory to conventional therapy. It has completely changed the treatment of this disorder. It is the sole substance that targets all involved pathophysiological factors in the disease: reduces sebaceous glands size, reduces production of sebum, normalizes cellular differentiation, and indirectly reduces *P. acnes* population. It also has anti-inflammatory properties that inhibit neutrophil chemotaxis (King et al. 1982; Leyden et al. 1986).

The recommended dose is 0.5–1 mg/kg/day over the course for 6–12 months, until the accumulated dose reaches 120–150 mg/kg. Other therapeutic schemes with lower daily intake can be efficient, provided that the full recommended dose is achieved. Patients with pretreatment nodules or macrocomedones have a higher risk of worsening their conditions (flare-up) as soon as they start taking isotretinoin. In these patients, it is advisable to start with lower doses (0.5 mg/kg/day or less) and increase them gradually to avoid worsening the initial inflammatory process. Oral corticosteroid prior to the treatment may be recommended. Isotretinoin should be administered during meals for better absorption (Layton 2009).

Even though it is the most effective drug in the treatment of acne, relapse occurs in at least 20% of the patients, most often in preadolescents, in people with cystic acne, with severe acne with crusted injuries, in patients with hyperandrogenism, and those taking lower doses during treatment.

Skin dryness, cheilitis, xerophthalmia, epistaxis, increased triglycerides, and transient worsening of acne are the most frequently observed adverse effects. The intensity of these effects is directly related to dosage. The absence of cheilitis in patients with therapeutic failure should raise the suspicion of non-compliance to treatment or malabsorption. Headache, arthralgia, myalgia, insomnia, elevated CPK, elevated liver enzymes, and decreased night vision are other possible adverse reactions (Montagner and Costa 2010). Hyperostosis, premature epiphyseal closure, and bone demineralization have been linked to high-dose isotretinoin schemes in patients with keratinization disorders or neuroblastoma, but these changes are not observed in the routine acne treatment (Eichenfield et al. 2013). Most side effects are transitory and cease after its discontinuation.

Isotretinoin is known to be teratogenic and, therefore, is classified as category X by the FDA. Exclusion of pregnancy before the beginning of the treatment, the compulsory use of two contraceptive methods throughout the period of administration and until 1 month after discontinuation are required (Montagner and Costa 2010; Murase et al. 2014).

Mood changes, depression, and suicidal ideas have been reported in patients using isotretinoin, but a causal relationship has not been established. It is important to highlight that severe acne itself may be a predisposing factor for psychiatric changes (On and Zeichner 2013; Borovaya et al. 2013).

There are conflicting reports that show an association between inflammatory bowel disease, particularly ulcerative rectocolitis, and isotretinoin. Even though there are some case reports, the occurrence seems to be rare, and there are no clinical characteristics that identify higher-risk patients (Etminan et al. 2013; Rashtak et al. 2014).

The most frequent laboratory changes are increasing of triglyceride levels and, to a lesser extent, cholesterol. Changes of liver enzymes can

be observed, generally mild and reversible. All patients should be subjected to a laboratory examination prior to starting treatment, and, although there is no consensus regarding the frequency of subsequent tests, a new laboratory test should be conducted 1–2 months after the therapy starts. In case of any abnormality, the tests should be repeated periodically. Female patients of childbearing age, albeit necessarily in use of contraceptives, should take pregnancy tests prior to starting treatment, monthly and 5 weeks after its completion.

In regard of drug interactions, tetracycline, minocycline, and doxycycline should be avoided, since their concomitant use favors occurrence of benign intracranial hypertension. Improper intake of alcohol reduces the effect of isotretinoin and can trigger headaches, malaise, and flushing, in addition to increase risk of hepatotoxicity. Vitamin A-containing supplements should be avoided due to risk of hypervitaminosis A. Levels of carbamazepine and phenytoin are reduced when administered together with isotretinoin, and they should be monitored in patients with epilepsy taking these medications concomitantly.

Patients with systemic diseases must be assessed carefully and may be treated with isotretinoin according to specific protocols that aim to minimize adverse effects with associated diseases. Depending on the underlying disease, the patient may be subjected to one of the three protocols developed by Cunliffe and Stables (Layton 2009).

Protocol A: patients with epilepsy, Crohn's disease, ulcerative colitis, diabetes mellitus, and spina bifida do not require dose adjustment and can be subjected to the usual treatment, taking into account laboratory control and attention to possible drug interactions.

Protocol B: chronic failure patients, with hypertriglyceridemia, purpura, immune suppression, obsessive-compulsive disorder, myalgic encephalopathy, motor neuron disease, and multiple sclerosis, should start treatment with half the usual dose, and, if there are no complications, dose can be increased every 2 months.

Protocol C: patients with rare diseases as Behcet's syndrome, spongiform cerebellar encephalopathy, idiopathic thrombocytopenia, leukemia, mitochondrial degeneration, paroxysmal nocturnal hemoglobinuria, and polymyalgia rheumatica. A weekly dose of 20 mg is recommended to initiate treatment. The dosage should be gradually increased, and after 7 weeks, it can reach 20 mg, twice a day.

Cosmetic Approach of Inflammatory Acne

Chemical Peelings

Superficial chemical peelings can be used as an adjuvant therapy in cases of comedonian or inflammatory acne until topical medical treatment starts to show some effect. This initial improvement of acne lesions reduces patient's anxiety which usually desire an immediate result. It also contributes to reduce postinflammatory hyperpigmentation.

We usually perform 20% or 30% salicylic acid peels or Jessner's solution peels or glycolic acid peels (35–70%; pH 2.75). Two or three sessions can be indicated as a monthly regimen or every 2 weeks, according to clinical response to standard topical treatment.

Salicylic acid has a lipophilic nature and a strong comedolytic effect. A study compared 30% salicylic acid peel in one side of the patient's face and Jessner's solution peel in the other side. The authors found that 30% salicylic acid peels were more effective than Jessner's solution peels for treating noninflammatory acne, although both showed efficacy for reducing inflammatory acne lesions. Salicylic acid superficial peel can be used in dark skin (Bae et al. 2013).

Lipohydroxyacid peels, a lipophilic derivative of salicylic acid with comedolytic properties, were performed in subjects with comedonal acne. The regimen was a total of six peels at 2-week intervals. They decreased the number of noninflammatory lesions as salicylic acid peels do, but not inflammatory lesions (Levesque et al. 2011).

Forty percent glycolic acid peels (pH 2.0), in a protocol of five sessions at 2-week intervals, were

performed in Asian skin in a placebo-controlled study. Glycolic acid peels significantly reduced noninflammatory and inflammatory acne lesions (Kaminaka et al. 2014). Some studies have demonstrated that glycolic acid chemical peels have growth inhibitory and bactericidal effects on *P. acnes* and that chemical peeling with glycolic acid works on inflammatory acne via those effects (Takenaka et al. 2012).

Erythema, scaling, and dryness for a few days are expected as for any superficial chemical peel, and these effects can be ameliorated by the use of moisturizers and regenerating creams or lotions.

Medium-deep peels are indicated for acne scars (described in Acne Scars section).

Light-Emitting Diodes: Blue Light

Previous observations have shown that patients experience acne improvement after exposure to natural sunlight, but the mechanism for this event had not been elucidated.

Light is produced when electricity is run through the semiconductor of the light-emitting diode (LED). The wavelength of light produced is dependent on the composition of the semiconductor chip. Depth of tissue penetration and the LED's target depend upon the wavelength of the light.

LEDs seem to affect cellular metabolism by triggering intracellular photobiochemical reactions (Opel et al. 2015). Blue LED light (400–470 nm) has a maximal penetration of up to 1 mm (Barolet 2008).

It has an effect on *P. acnes* in acne vulgaris since this microorganism contains naturally occurring porphyrins within sebaceous follicles and blue LED light has anti-inflammatory properties on keratinocytes. Absorption of the light is believed to induce a natural photodynamic therapy which leads to acne improvement. Porphyrins absorb light wavelengths between 400 and 700 nm, and 415 nm wavelength within the blue light spectrum is the most effectively absorbed.

Thiboutot et al. reviewed eight studies published between 2000 and 2006 about blue light treatment of mild-to-moderate acne and found moderate evidence in support of its efficacy, especially for inflammatory lesions (Thiboutot et al. 2009).

Morton et al. treated 30 patients with mild-to-moderate acne with blue LED (415 nm) treatments for 1 month. Mean inflammatory lesion counts decreased with minimal effect on non-inflammatory lesions (Morton et al. 2005). The results of their study were similar to Tremblay's which treated mild to moderate inflammatory acne patients with two sessions a week of 20-min treatments of blue LED light (415 nm) for 1or 2 months. Patients had at least 50% reduction in lesions counts, and some patients were totally clear (Tremblay et al. 2006).

Although most studies on blue light were small and open-label trials, a more recent double-blind and randomized controlled study using blue-red light therapy found reduction of inflammatory and noninflammatory acne comparable to earlier open-label trials. Moreover, decreased production of sebum and sebaceous gland size was noted (Kwon et al. 2013).

More trials comparing blue light therapy with conventional acne treatments such as topical retinoids and antibiotics are needed. Considerations of this modality of therapy are long-term benefits, time of lesions remission, and adverse effects.

Photodynamic Therapy (PDT)

Photodynamic therapy combines the application of photosensitive substances and subsequent activation by light source with consequent generation of cytotoxic oxygen species (and possibly free radicals) to promote the selective destruction of target tissues. The light is absorbed by the photosensitive agent (which may be a colorant, a hematoporphyrin derivative, or "prodrug" protoporphyrin). Reactive oxygen species capable of damaging cellular components are generated (Nestor et al. 2006).

A suitable combination of the photosensitizing agent or dye and a light source with known

wavelength that occurs for the desired cell damage is needed.

Aminolevulinic acid photodynamic therapy is used as an *off-label* treatment of inflammatory acne, although it is widely used in the USA. There are no satisfactory clinical responses to comedonian acne.

Clinical trials have demonstrated improvement not only of inflammatory lesions of acne but also in decreasing the size of the sebaceous gland, causing photodynamic death of *Propionibacterium acnes* (which absorbs ALA with production of PpIX), keratolysis, and reduction of production of sebum (Santos et al. 2005). Histological analysis showed destruction of the sebaceous glands, suggesting that this therapy has the potential to induce a remission of acne for a long term. There is follow-up showing remission of up to 13 months (Alexiades-Armenakas 2006).

Those studies used blue light or IPL (intense pulsed light) as the light source. The incubation time of ALA for acne is 30–60 min. Multiple sessions are needed to get a satisfactory result. However, the exact number of sessions required for optimal treatment has not been established nor was defined the most appropriate source of light. The used lights are blue or red. Another aspect is the incubation time that was not fully stablished. However, as the sebaceous glands are in the middle dermis, it is possible that the red light is a better choice to achieve these glands.

It was presented at the *American Academy of Dermatology Congress* in 2008, a PDT protocol for acne associated with microdermabrasion followed by 10 min of 5-ALA incubation, and it was shown to be effective as PDT with 1 h incubation of ALA (Be 2008).

In Europe, as the main focus of the methyl aminolevulinate photodynamic therapy (MAL-PDT) is skin cancer nonmelanoma, scientific studies about PDT use in acne are scarcer. In 2008, it was presented in Spain a Brazilian study with five patients treated with PDT using methyl aminolevulinate Metvix® (three sessions with an interval of 1 month) showing 60% reduction in the number of inflammatory lesions. The interesting aspect was the remission of acne up to 6 months, but transient post-inflammatory hyperpigmentation may occur (Torezan et al. 2008).

As acne is a multifactorial disease, PDT should not be used as monotherapy acne, but combined with antibiotics, antiandrogen medications, and topical retinoids. For patients with moderate to severe inflammatory acne with contraindication or restriction of the use of oral isotretinoin, PDT can be used.

As side effects of PDT for acne, we can expect transient hyperpigmentation, superficial exfoliation, and crusting, which usually resolve without scarring.

Intense Pulsed Light

Intense pulsed light (400–1,200 nm) devices employ flashlamps and band pass filters that produce polychromatic incoherent high-intensity pulsed light. Absorption of light can activate porphyrins that reduce *P. acnes* growth. Other chromophores (such as hemoglobin) in the skin absorb light delivered by IPL, and this treatment can reach blood vessels that supply sebaceous glands, thus reducing sebaceous gland size and/or function. IPL may also exert an anti-inflammatory effect through downregulation of tumor necrosis factor alpha (TNF-α) (Taylor et al. 2014).

Reported efficacy of IPL for acne treatment ranged from 34% to 88% improvement depending on acne type (inflammatory or noninflammatory) in a systematic review of the use of IPL in acne patients (Wat et al. 2014).

An advantage of IPL treatment is the improvement of erythema secondary to inflammatory lesions, hyperpigmentation, and uneven skin tone. A careful selection of the patient (avoid high fluences in dark skin patients) is important to avoid undesirable effects such as burning or worsening of hyperpigmentation.

A few studies have compared IPL alone versus conventional therapies. Nevertheless, the aim of treatment is to combine techniques and topical/oral treatment to achieve the best results.

Acne Scars

Acne is a very common condition which often results in formation of scars. Appropriate and early treatment is the best way to prevent their occurrence. However, despite all therapeutic efforts, the occurrence of scars is often inevitable (Layton 2009; Rivera 2008).

The first step of the treatment is to establish the kind of scars, the severity of injuries, goals, and expectations, making clear that depending on the condition, complete disappearance of the scar may not be feasible and that the goal of the treatment is to obtain a significant improvement.

Acne scars can be prominent (hypertrophic, keloidal, papular, and bridges), dystrophy, and depressed (expandable and nonexpandable). Depressed scars are the most frequent, and the subclassification described by Jacob *and col* included ice pick, rolling, and boxcar scars (Rivera 2008; Jacob et al. 2001; Goodman and Baron 2006).

A classification based on the severity of the scars was described by Goodman and Baron, in which four degrees of severity of the condition are considered. They can be macular, mild, moderate, and severe (Goodman and Baron 2006).

Multiple treatments have been described such as peelings, microdermabrasion, dermabrasion, fillings, subcision, excision and suture, punch excision, needle incision, radiofrequency vaporization, microneedling, fractional ablative radiofrequency, lasers, and other light sources.

In general, hypertrophic scars can be treated by tangential or total excision, intralesional corticosteroid infiltration, or intense pulsed light. Expandable depressed scars can be treated by means of fillings or they must be submitted to subcision when there is scar retraction. Superficial nonexpandable depressed scars can be addressed through dermabrasion, chemical abrasion, and laser resurfacing. In cases of medium or crateriform scars, their edges are raised or lowered, whether or not followed by ablasive procedures. For deep fibrotic scars in ice picks, total skin grafts can be made with a punch harvested from the preauricular, infra-auricular, or retroauricular or the CROSS method.

Peelings

Chemical peelings can be used both for treatment of scars as well as for acne injuries. Superficial peelings such as glycolic, citric, lactic, and salicylic acids, Jessner's solution, modified Jessner's solution, resorcinol, and low concentrations of TCA (<10%) are beneficial for mild scars. Medium peelings such as TCA solutions between 10% and 40% can be used with good results, but the risk of pigmentary changes and scarring increases in proportion to concentration.

The CROSS method (chemical reconstruction of skin scars) with focal application of TCA 65–100% is an alternative for crateriform deep scars and ice picks and can be applied intralesionally, four to six times, monthly (Lee et al. 2002). Deep peelings such as phenol can bring more consistent results, despite the greater potential for side effects. It is important to be aware of possible phenol cardiotoxicity (Landau 2005).

Dermabrasion

While microdermabrasion is a quite superficial procedure, which requires multiple sessions and brings more benefits in texture than scarring changes, dermabrasion is a far more effective therapy, since it promotes the removal of the skin surface and determines the improvement in refined borders of scars. The procedure aggressiveness is related to possible adverse effects which include erythema and prolonged healing time, milia, viral or bacterial infection, hypertrophic or keloidal scars, telangiectasias, hyperpigmentation, and prolonged or permanent hypopigmentation. The procedure is painful and requires local or regional anesthesia.

Fractional Ablative Radiofrequency

Fractional ablative radiofrequency uses a high-frequency current, distributed by a fractional tungsten tip, whose target is the intracellular water. It is a lower-cost alternative.

Microneedling

Microneedling is the latest technique which has been showing good results. It consists in the use of a portable instrument, covered by micro-needles of 0.07 mm thick and 0.25–2.5 mm long, and it aims to cause micro-channels in the skin to produce collagen and neovascularization or to facilitate the introduction of drugs into the dermis (drug delivery). The procedure is carried out with topical anesthesia, and the equipment is applied to the skin from 15 to 20 times in the selected area, to produce bloody dew (pinpoint). Generally three to six sessions are indicated in 8–10 weeks intervals. Since it is a technology-dependent procedure, familiarity with the instrument used and the mastery of the technique are factors that directly influence the final outcome (Doddaballapur 2009; Fabbrocini et al. 2009; Lima and Lima 2013).

Fractional Lasers

Ablative CO2 laser was considered the gold standard for correction of scars such as ice picks or depressed ones for a long time. However, due to complications and recovery time, their use was gradually replaced by the current non-ablative fractional lasers, such as Erbium 1,540 nm, Erbium 1,550 nm, NdYAG: 1,440 nm or fractional ablative ones such as CO2 10,600 nm, and Erbium YAG 2,940 nm. They promote thermal insult to dermis microzones, whereas ablative lasers also promote it to epidermis microzones, leading to collagen contraction and neocollagenesis. Generally, it takes from two to three sessions, and the results can be quite satisfactory (Goodman 2011).

Currently, we have a wide therapeutic arsenal for the treatment of acne scars. Even though equipments as well as increasingly sophisticated and safe techniques have been developed, prevention and control of acne injuries are still the best option for these patients.

Rosacea

Pathogenesis of Rosacea

The exact pathogenesis of rosacea is not fully understood. One of the most important etiopathogenic factors is an aberrant dysregulation of the innate immune system. Microorganisms may contribute to rosacea occurrence by stimulating this particular part of the immune system. Abnormal vascular and nervous skin responses are observed in rosacea patients (Schauber 2011).

Dysregulation of Innate Immune System

Recent evidence has supported the role of increased levels of a trypsin-like serine protease Kallikrein 5 (KLK5) as a promoter of augmented inflammatory response in rosacea. These increased levels of KLK5 resulted in great quantity of cathelicidin (LL-37), an antimicrobial peptide associated with vasodilation, and vascular proliferation that are characteristic features of rosacea (Two and Del Rosso 2014). In addition to being more abundant, the forms of KLK5 and LL-37 present in rosacea skin differ from those in normal healthy skin (Yamasaki et al. 2011). Therapeutic interventions that modulate the effects of Kallikrein 5 may improve rosacea symptoms.

Besides cathelicidin expression in keratinocytes is strongly induced by vitamin D, which is activated in keratinocytes by UV radiation, a known trigger of rosacea (Schauber 2011). Augmented levels of TLR2 were found in lesional skin of patients with rosacea. Triggers for TLR2 are typically structural molecules on the cell wall of microbes, and these stimuli may include chitin released from Demodex mites and lipoproteins from the Demodex-associated Gram-negative bacterium (Koller et al. 2011).

Activation of Th1/Th17 Pathways

Buhl et al. have shown significant activation of the immune system in rosacea. Erythematotelangiectatic rosacea is a disease with significant influx of pro-inflammatory cells. Chemokine expression patterns supported a Th1/Th17 polarization profile of the T-cell response with increase of macrophages and mast cells. In patients with papulopustular rosacea, many neutrophils were also observed. The knowledge of Th1/Th17 polarized inflammation and macrophage infiltration as hallmarks of all subtypes of rosacea may lead to the development of therapies targeting the Th1/Th17 pathway (Buhl et al. 2015).

Microorganisms

Additional evidence that *Demodex folliculorum* may contribute to the pathogenesis of papulopustular rosacea are studies of topical antiparasitic agents. Ivermectin and praziquantel have recently been shown to be effective in decreasing the severity of papulopustular rosacea. If Demodex plays a role in pathogenesis, then hypersensitivity to the mites, or their products, might explain the efficacy of antidemodectic therapy (Ali et al. 2015).

Individuals with rosacea have been shown to have a higher density of Demodex mites on their facial skin compared to individuals without rosacea suggesting that these mites may have played a role in rosacea pathogenesis (Jarmuda et al. 2012). These mites release chitin, which activate toll-like receptor 2 of keratinocytes and elicit an innate immune response (Ferrer et al. 2014).

Another aspect is that the erythroid differentiation regulator 1 (Erdr1) is downregulated in patients with rosacea and it may be involved in attenuating the inflammation and angiogenesis. Treatment with recombinant Erdr1 (rErdr1) resulted in a significant reduction of erythema, inflammatory cell infiltration, and microvessel density (Koller et al. 2011; Kim et al. 2015).

Ultraviolet Radiation Effect in Rosacea

UV radiation produces flushing and can worsen clinical findings of rosacea. It is known that ultraviolet radiation results in production of reactive oxygen species (ROS) in the skin. These high levels of ROS promote a pro-inflammatory response, through TLR2 receptors, propagating the KLK5 cathelicidin cascade (Bakar et al. 2007).

Abnormal Barrier Function

Some studies have demonstrated increased transepidermal water loss and decreased epidermal hydration not only in erythematotelangiectatic rosacea but also in papulopustular subtype (Dirschka et al. 2004). Besides reduced epidermal hydration, rosacea patients have a more alkaline centro-facial region (Ni Raghallaigh and Powell 2014). One explanation for this decreased barrier function is increased serine protease level which is associated with PAR2 activation and disturbance of barrier homeostasis. The use of a topical serine protease inhibitor accelerated barrier recovery after an acute exacerbation of rosacea (Hachem et al. 2006; Leyvraz et al. 2005).

Vascular and Nervous Dysregulation

Some studies have demonstrated vascular changes and abnormal nervous response to environmental triggers. One finding is that hyperthermia by vasodilation is thought to be exaggerated in rosacea patients (Steinhoff et al. 2013).

Facial flushing is a hallmark of rosacea and is possibly caused by increased flow to blood vessels which are closer to the surface of facial skin (Guzman-Sanchez et al. 2007). It is often induced by trigger events such as heat and ingestion of spicy food. Some data indicated that rosacea affects sympathetic nerve activity since there is a hyperresponsiveness to these trigger factors with a sympathetic component. Heat stress induced more rapid sweating and cutaneous vasodilation onset in rosacea compared with controls. Skin sympathetic nerve activity was augmented in rosacea patients during mental and physical stress (Metzler-Wilson et al. 2015).

Clinical Classification of Rosacea

Rosacea occurs in both men and women, although it is more prevalent in women than in men. However, men with the condition are more likely to develop phymatous changes. It is more frequent in patients with fair skin and affects mostly adults.

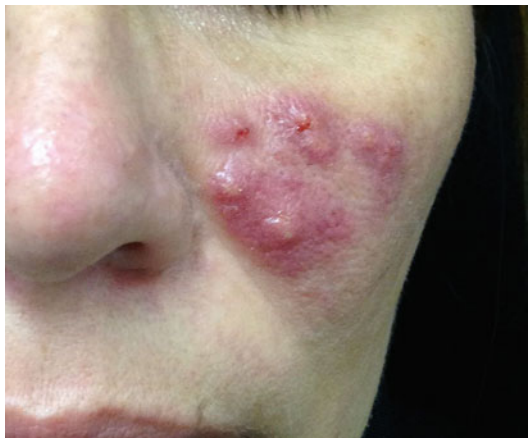

Fig. 4 Papulopustular Rosacea

Children appear rarely affected (Elewski et al. 2011).

At past, Rosacea was called "acne rosacea," but the form that was described is actually papulopustular rosacea.

Most authors agree on four major clinical types of rosacea (Elewski et al. 2011):

- **Erythematotelangiectatic rosacea** (**ETR**): characterized by persistent central facial erythema, flushing, and telangiectasias. Burning or scaling may be associated.
- **Papulopustular rosacea** (**PPR**): characterized by erythematous papules and pustules besides telangiectasias and flushing (see Fig. 4).
- **Phymatous rosacea**: thickened skin with enlarged pores associated with tissue hyperplasia and nodules – sebaceous glands hyperplasias (called *phymas*). They occur over the ears, chin (gnathophyma), forehead (metophyma), and nose (rhinophyma).
- **Ocular rosacea**: Ocular manifestations depend on the type of rosacea. Ocular chronic inflammation, ulcerations, and nodular infiltrates may be present. An associated skin rosacea may occur or not be present.

We must be aware that patients with easy skin irritation, flushing, and transient erythema may be rosacea-prone patients.

There is a special form called **granulomatous rosacea** characterized by firm periorificial or malar yellowish, erythematous, or brownish papules and nodules.

Diet and Rosacea

It is critical to address the importance of an adequate diet in rosacea patients. The excessive intake of processed and ready-to-use food and hot beverages is traditionally thought to trigger flushing in patients with rosacea. There are many triggers that are present in a common diet: caffeine, alcohol, spicy foods, and hot drinks (Elewski et al. 2011; Two et al. 2015b). Most evidence does not support that the dietary factors play a central role in the pathogenesis, since they are triggers and not causes of the disease. Nevertheless those potential provokers must be avoided to optimize treatment.

Considering vitamin supplementation, high intake of vitamins B6 and B12 may cause flares for patients with rosacea (Elewski et al. 2011).

The link between diet and rosacea is not recent. Since 1970, dermatological medical articles have suggested an association between some inflammatory skin diseases and gut – inflammatory gastrointestinal tract disorders (Fry 1970). Confirming this connection, in 2004, Kendall described the case of a patient without digestive tract disease who experienced complete remission of rosacea symptoms following ingestion of a material intended to sweep through the digestive tract and reduce transit time below 30 h. He suggested that it is possible that intestinal bacteria are capable of plasma Kallikrein-kinin activation (as described at *Pathogenesis* Section) and that flushing symptoms may result from episodes of neurogenic inflammation caused by bradykinin-induced hypersensitization of facial afferent neurons (Kendall 2004).

Treatment of Rosacea

Rosacea treatment consists of measures to control and achieve clinical remission, improving the quality of life and psychosocial effects for patients affected by this disease. Depression and low self-esteem are more prevalent in these patients when

compared with general population (Two et al. 2015b; Gupta et al. 2005).

A variety of both topical and systemic treatment options are available for these patients; however, patient education and routine skin care are also important aspects of treating rosacea.

FDA-approved treatments for rosacea are oral doxycycline 40 mg/day and topical drugs such as metronidazole, azelaic acid, sodium sulfacetamide/sulfur, brimonidine, and, more recently, ivermectin.

In this chapter, we try to include all therapeutic approaches reported in the literature, FDA approved or non-FDA approved, but which have been used in some trials, especially in patients refractory to conventional treatment. Thus, treatment for rosacea has been split considering the following aspects: removal of aggravating causes, topical medications, systemic medications, lasers/IPL/PDT, and the current perspectives on botulinum toxin en ETR treatment.

Removal of Aggravating Causes

Initially, it's important to identify and rule out all causes that may trigger or exacerbate disease symptoms and signs. As these factors are specific to each patient and are not necessarily identified, a thorough search is necessary as a first therapeutic approach. Several cosmetic formulations dry and damage skin, which probably emanates from vascular hyperreactivity or barrier dysfunction. In addition, irritating topical substances such as menthol, camphor, toners, astringents, exfoliators, and alcohol-based products containing sodium laurel sulfate or products that impair their barrier function such as waterproof cosmetics and thicker foundations that are difficult to remove may worsen clinical condition, and their use should be avoided. Rosacea patient skin is sensitive to many substances, including surfactants and fragrances used in some soaps and cleaning lotions, which should be soft and applied with the fingers to minimize skin aggression.

Avoiding such products is not always effective, since often the chemical interaction or concentration, and not actually itself, is the cause of skin irritation. Liquid foundations, preferably containing silicone associated with a broad-spectrum sunscreen, are best suited for being softer.

Cosmetic camouflage, especially in yellow and green shades, is a helpful method in covering and concealing erythema/redness and, hence, providing psychological benefit to rosacea patients.

Acute ultraviolet (UV) light exposure is known as trigger to rosacea symptoms because it stimulates LL-37 production and has been suggested to deplete antioxidant reserves in the skin and increase the production of relative oxygen species (ROS). The use of broad-spectrum sunscreen use is highly recommended, and physical blockers containing titanium dioxide and zinc oxide are best tolerated for those who often have sensitive skin. In some cases, sunscreens may irritate skin and trigger erythema. Silicones in the form of dimethicone or cyclomethicone should be added to filters as protective agents to minimize these adverse effects (Pelle et al. 2004).

Many patients often make exposure of topical corticosteroids prescribed by professionals in the first stage of the treatment in an attempt to minimize the persistent symptoms like flushing, erythema, papules, pustules, and telangiectasias. Once rosacea diagnosis has been confirmed, promptly discontinue is of the utmost importance because although there is a worsening of clinical symptoms due to corticosteroid withdrawal, the improvement will not be achieved until its discontinuation.

Topical Therapy

The main agents used in topical treatment are:

- Alpha-adrenergic receptor antagonists: Brimonidine gel 0.5% (alpha-2 adrenergic receptor agonist) was proved to be effective in reducing persistent facial erythema, by vasoconstricting dermal blood vessels (Elewski et al. 2011; Weinkle et al. 2015; Del Rosso et al. 2014a). Clinical trials have shown a reduction in baseline facial erythema in as few as 30 min after application of the gel, with maximal erythema reduction lasting between

6 and 7 h after a single application. After this time, the patient's erythema scores returned to baseline (Two et al. 2015b; Del Rosso 2013; Tanghetti et al. 2015). There have been very few reports of rebound erythema and contact dermatitis in the literature, and new studies are required for a better understanding between an actually rebound or just a therapeutic failure (Werner and Kobayashi 2015). Another drug, oxymetazoline 0.05%, a selective alpha-1-adrenergic receptor agonist, has been described as effective in reducing erythematotelangiectatic rosacea (Elewski et al. 2011; Del Rosso 2013; Shanler and Ondo 2007). These agents do not impact on telangiectasias, nor do they affect inflammatory lesions.

- Metronidazole: cream or gel at concentrations of 0.75 and 1% once or twice daily has been used for years in papulopustular rosacea treatment. Despite being an antibacterial and antiprotozoal agent, therapeutic benefits are mostly derived through its anti-inflammatory and antioxidant effects (Elewski et al. 2011). The clinical efficacy of metronidazole has been attributed to its ability to decrease ROS generation and inactive existing ROS production (Two et al. 2015b).
- Azelaic acid: cream, gel, or foam at concentrations of 15 or 20% b.i.d. has anti-inflammatory, antioxidant, and antimicrobial effects (Elewski et al. 2011; Two et al. 2015b). More recent studies suggest that this medication decreases expression of both Kallikrein 5 and cathelicidin, directly target to rosacea's pathogenesis (Two et al. 2015b).
- Sodium sulfacetamide/sulfur: due to its antibacterial, antifungal, keratolytic, and anti-inflammatory effect, cleansers, lotions, and creams containing sodium sulfacetamide 10% and sulfur 5% are classically used in papulopustular rosacea, especially in clinical features where there are concomitant seborrhoeic dermatitis (Elewski et al. 2011; Two et al. 2015b).
- Antiparasitic agents: ivermectin topical cream 1% once daily has been the most recent medication approved by the FDA for use in Rosacea and has both anti-inflammatory and antiparasitic properties. Some studies have shown better efficacy in disease control when compared to metronidazole and azelaic acid. However, a longer period of assessment will be required to confirm data (Layton and Thiboutot 2013; Stein Gold et al. 2014; Gollnick and Layton 2008; Abokwidir and Fleischer 2015). Other anti-demodex agents such as permethrin 5% and crotamiton 10% have been studied as controllers of *Demodex folliculorum* and *D. brevis* (Layton and Thiboutot 2013).
- Antibiotics: topical erythromycin 2% and clindamycin phosphate 1%, used singly or associated with benzoyl peroxide 5%, are therapeutic options due to their anti-inflammatory action.
- Topical retinoids: tretinoin and its derivatives adapalene and tazarotene are considered *off-label* when used in the treatment of rosacea. Their indication is still limited as they are potentially skin-irritant. The mechanism of action is related to connective tissue remodulation and TLR2 downregulation (Two et al. 2015b).
- Topical calcineurin inhibitors: tacrolimus and pimecrolimus are immunomodulators used singly or associated with oral medications to treat rosacea-like eruptions triggered by corticosteroids (Pelle et al. 2004; Chu 2007). The ability to inhibit T-cell and mast cell activation, avoiding the release of pro-inflammatory cytokines, is likely to be their mechanism of action (Two et al. 2015b; Weissenbacher et al. 2007; Nally and Berson 2006).
- Cyclosporine an ophthalmic emulsion: a concentration of 0.05% is used in ocular rosacea treatment as it inhibits T-cell activation and inflammatory cytokine induction in the conjunctiva (van Zuuren et al. 2011).

Oral Therapy

The following systemic substances are used in Rosacea:

- Tetracyclines: tetracyclines have been used for years for therapy of PPR and are managed continuously for a period of up to 6 months.

Minocycline 100 mg (b.i.d.) and doxycycline 100–200 mg/day are better tolerated derivatives. Despite their wide use, antibiotics can lead to selection of bacterial pathogens. *Sub-antimicrobial dose doxycycline* (SDD 40 mg/day), approved as a therapy for patients with rosacea, offers anti-inflammatory action (by reduction of MMPs and consequent decrease in KLK5, besides reducing the inflammatory cytokines), with no impact on bacterial resistance according to current studies (Two et al. 2015b; Layton and Thiboutot 2013; van Zuuren et al. 2011; Del Rosso et al. 2007, 2014b; Baldwin 2012; Fowler 2007).

- Macrolide antibiotics: in cases of patients with allergy and intolerance or resistance to tetracyclines, patients who are pregnant or breast-feeding, and children under 12 years of age, the drug of choice is erythromycin. Clarithromycin and azithromycin, second-generation macrolides, also present effective systemic action in the treatment of rosacea.
- Metronidazole: 200 mg b.i.d. for 6–12 weeks can be considered as an alternative for patients who do not respond well to tetracyclines.
- Isotretinoin: it is an effective and indicated drug for patients with severe disorders of granulomatous rosacea and recalcitrant papulopustular rosacea. Based on the significant reduction of TLR-2, the treatment consists of daily doses ranging from 0.5 to 1 mg/kg. However, more recent studies indicate that lower doses, such as 10 mg/day, also show good clinical response, with minimal adverse effects, and are well tolerated. Isotretinoin should neither be administered associated with oral tetracyclines due to the risk of developing pseudo brain tumor nor in other clinical indications (Two et al. 2015b; Rallis and Korfitis 2012; Rebora 2002). The safety profile of isotretinoin in rosacea is similar to that seen of *acne vulgaris*, and therefore routine safety and laboratory monitoring is required.
- Beta-blockers: they have been shown to decrease erythema and flushing in some rosacea patients, by inhibiting beta-adrenergic receptors on the smooth muscles surrounding blood vessels, leading to vasoconstriction of these vessels. As they reduce sympathetic activity, they act in flushing, especially in patients that show anxiety as comorbidity. Hypotension and bradycardia are frequent undesirable adverse effects associated with those medications, especially in normotensive individuals. Some studies have indicated anti-inflammatory and antioxidant effects of carvedilol, which consequently decrease in facial erythema, showing no side effects related to hypotension and bradycardia (Two et al. 2015b; Layton and Thiboutot 2013; Del Rosso et al. 2014b).
- Clonidine: this adrenergic agonist is also effective in the treatment of facial flushing. It usually does not cause changes in blood pressure when prescribed at the dose of 0.05 mg b.i.d. (Baldwin 2006).
- Oral ivermectin: the use of this broad-spectrum antiparasitic is especially indicated for immunocompromised patients with rosacea-like demodicosis (Layton and Thiboutot 2013).
- Dapsone and zinc sulfate: some reports show that these substances were occasionally used in the cases of Rosacea, but are no longer used actually.

Laser and Intense Pulsed Light (IPL)

The control of rosacea signs and symptoms can be achieved through therapies based on lasers and intense pulsed light, since both are capable of acting on PPR and ETR (Butterwick et al. 2006). The type of light to be used depends on disease clinical manifestation, which occurs by the capacity of light absorption by hemoglobin. Thus, lasers with shorter wavelengths such as the pulsed dye laser (PDL) and the potassium titanyl phosphate (KTP) laser can be used for the treatment of superficial red veins and persistent erythema, whereas lasers with longer wavelengths such as the 810 nm diode laser, the 755 nm alexandrite LP, and the 1,064 nm Nd: YAG LP can be used to reach face deeper blue veins (Tanghetti et al. 2014; Mansouri and Goldenberg 2014).

Ideal laser for treating dermal vessels is the 585 or 595 nm pulsed dye laser (PDL), long

pulse and circular or oval spot size. The main drawback is the possibility of developing residual purpura. The KTP 532 nm laser with longer pulse duration can avoid this cutaneous vascular damage. However, it has a shorter wavelength than the PDL and therefore a less profound effect on the vascular system. Its use in higher phototypes requires particular attention, since post-inflammatory hipercromia represents an undesirable risk in this group due to a greater capacity melanin absorption. Combined treatments with 1,064 nm Nd: Yag and 595 nm PDL have been satisfactorily used for facial telangiectasia treatment.

Intense pulsed light devices produce non-coherent light ranging in wavelengths from 500 to 1,200 nm. It has the advantage of lower cost and the possibility of treating different sizes of veins at various depths simultaneously, according to the filter used and the selected parameters. Shorter wavelength devices should also be avoided in tanned and dark-skinned patients due to the interaction with melanin (Tanghetti et al. 2014; Butterwick et al. 2006; Mansouri and Goldenberg 2014).

Photodynamic therapy (PDT) can be used in the treatment of rosacea, especially in patients with actinic damaged skin, but its exact mechanism of action remains unclear. PDT involves the topical application of a photosensitizing agent (5-ALA, MAL) followed by exposure to blue or red light (Butterwick et al. 2006; Mansouri and Goldenberg 2014).

Even though laser or intense pulsed light are effective, it is essential to observe that they will neither lead to a definitive clinical remission nor to the cure for rosacea. In addition to the usual treatments, a standard therapeutic protocol should include maintenance therapy every 4–6 months, since rosacea is a chronic and intermittent disease.

Botulinum Toxin

Further investigation is necessary to elucidate its mechanism of action, but it seems to be related to a neurogenic component associated with vascular dysfunction, inflammation, and sebum hyperactivity.

Intradermal injections of botulinum toxin, using microdrips, were applied, and 1 cm space between them was left so as to cover the entire erythematous area affected. They were applied in two sessions at weekly intervals, having shown a meaningful response which lasted a few months. Randomized studies are still required to assess its clinical application (Dayan et al. 2012; Bloom et al. 2015; Park et al. 2015).

Rhinophyma

The treatment of phymatous changes, particularly rhinophyma, is eminently surgical, and no consensus on an ideal approach has been achieved. Cryosurgery, dermabrasion, surgical excision, electrosurgery, radiofrequency electrosurgery, and fractional laser are some treatment options (Tanghetti et al. 2014).

Take-Home Messages

- Acne vulgaris is a chronic inflammatory disorder of the pilosebaceous unit with a multifactorial pathogenesis and a highly variable morphology. Recent evidence has emphasized the role for inflammation at all stages of acne lesion development.
- Acne treatment combines topical therapy, oral medication, and/or cosmetic procedures. Superficial chemical peels, phototherapy (blue light and intense pulsed light), and photodynamic therapy can be used as an adjuvant treatment of inflammatory lesions.
- Acne scars can be reduced by medium and deep peels, dermabrasion, microneedling, and fractional ablative lasers.
- The diagnosis of rosacea is based on clinical manifestations, but atypical cases may be misdiagnosed.
- FDA-approved treatments for rosacea are oral doxycycline and topical drugs such as metronidazole, azelaic acid, sodium sulfacetamide/sulfur, brimonidine, and, more recently, ivermectin.

Cross-References

- Chemical and Physical Sunscreens
- Cleansers
- Cosmeceutical Ingredients: Botanical and Non-botanical Sources
- Hydroxy Acids
- Nutraceuticals in Dermatology
- Oral Photoprotection
- Photoprotection: Concept, Classification, and Mechanism of Action
- Retinoids
- Vitamins and Other Antioxidants

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Cosmetic Approach for Melasma

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Abstract

Melasma is a chronic acquired focal hypermelanosis localized on sun-exposed areas that commonly affects females during their fertile years. Despite many known risk factors as cumulative sun exposure, oral contraceptive pills, pregnancy, stress, cosmetics, and some drugs, the physiopathology of melasma is not yet fully understood, which limits the development of definitive treatments and prevention strategies. Family occurrence (40–60%) is an evidence of genetic predisposition. Here, we discuss the role of sun protection, topical bleachers, light technologies, peelings, and oral strategies on therapeutic approach of melasma. Moreover, prognostic factors are pointed out.

Keywords

Melasma • Melanosis • Contraceptives • Oral contraceptives • Pregnancy • Hormones • Chloasma • Gonadal steroid hormones • Melanosis • Pigmentation • Skin pigmentation • Ultraviolet rays • Pigmentation disorders

Contents

Introduction

Melasma is a chronic and acquired localized hypermelanosis, which affects mainly women of intermediate phototypes during fertile age (Miot et al. 2009).

It is characterized by symmetrical brownish macules with irregular edges and well-defined contours, mainly on the zygomatic, frontal, upper lip, nose, and chin. Less often, it affects

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extrafacial areas like the neck, arms, and anterior chest (Tamega Ade et al. 2013).

Melasma is a common disease in dermatological practice. In a Brazilian dermatologic survey, pigmentary diseases were the main cause of search for dermatologic care (Lupi et al. 2010). Studies in Nepal and Saudi Arabia indicate melasma as the fourth most frequent diagnosis (Alakloby 2005; Walker et al. 2008).

It occurs in all ethnic and population groups; however, epidemiological studies have reported higher prevalence among more pigmented phenotypes, such as East Asian, Japanese, Korean and Chinese, Indian, Pakistani, Middle Eastern, and African peoples. In the Americas, it is common among Hispanics and Brazilians who inhabit tropical areas, where there is increased chronic exposure to ultraviolet radiation (Handel et al. 2014b).

Although it can affect both sexes, melasma occurs more often in women in a ratio of 9–10:1. An Indian study identified a less impressive ratio (6:1); already in Brazil and Singapore, there were most notable predominance, 39:1 and 21:1 (Achar and Rathi 2011; Goh and Dlova 1999; Hexsel et al. 2014).

Among men, sexual steroids are not involved in most cases, but the report of intense sun exposure is imputed as main trigger factor. There is no clinical or histopathological characteristic that leads to consider as a different disease than melasma in women (Sarkar et al. 2010; Vachiramon et al. 2012; Vazquez et al. 1988).

There is no consensus on the clinical classification of melasma; most authors divide it as centrofacial and peripheral. The centrofacial type includes the cases that lesions are predominant in the center of the face or front, glabellar, nasal, zygomatic, upper lip, and chin. The peripheral melasma corresponds to impairment of frontoparietal regions, pre headset, and along the branches of the mandibulae (Tamega Ade et al. 2013).

There are several factors involved in the development of melasma, such as sun exposure, pregnancy, oral contraceptives and other steroids, ovarian tumors, hormone replacement therapy, cosmetics, photosensitizing drugs, inflammation, and stressful events. In addition, genetic predisposition is suggested by high familial incidence reports (40–60%). This evidences that melasma is a multifactorial disease and depends on the interaction of environmental and hormonal elements within a susceptible genetic substrate (Handel et al. 2014a).

Sun exposure is the main risk factor for melasma, exerting role both in its appearance as in worsening and maintenance. There is a clear improvement of melasma in the winter months and the aggravation in the summer periods and intense sun exposure. Moreover, the use of high-spectrum sunscreen reduces disease severity by 50% and decreases its effect on pregnancy in more than 90% (Lakhdar et al. 2007; Miot and Miot 2009).

In a Brazilian study with 302 patients with facial melasma, 48.5% reported intense sun exposure as a trigger. Another study showed that residents of rural and coastal areas had a higher frequency of facial melasma, evidencing the role of chronic sun exposure in disease development (Handel et al. 2014a; Tamega Ade et al. 2013).

Physiopathology

The physiopathology of melasma is not yet fully understood. Compared with the adjacent epithelium, there is greater melanin synthesis with higher yields and more mature melanosome transfer for all layers of the epidermis (Miot et al. 2010).

Melanocytes are hypertrophied with dendrites and most prominent organelles. Keratinocytes also express phenotypic changes such as changes in chromatin and organelles. This suggests that the pathophysiological process involves not only the melanocytic hypertrophy but the whole epidermal-melanin unit (Brianezi et al. 2015).

There are some alterations in the upper dermis such as collagen degradation; solar elastosis; damage in the basal membrane; presence of mastocytes, $CD4^+$ lymphocytes, and $CD68^+$ macrophages; and activity of MMP1, MMP2, MMP3, and MMP9. These findings suggest that a chronic inflammatory process can stimulate and maintain melanogenesis independently of sun exposure, as occurs in post-inflammatory pigmentation (Kang

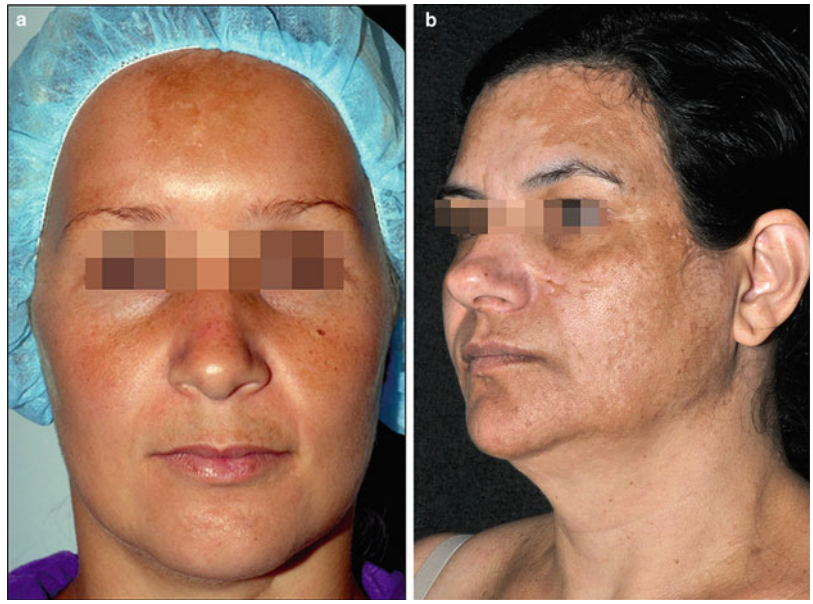

Fig. 1 Melasma. Predominantly centrofacial (**a**): zygoma, labial superior frontal, and glabella. Predominantly peripheral (**b**): frontoparietal, temporal, parotid, and mandibular rami

2012; Passeron 2013; Rodriguez-Arambula et al. 2015).

Some inflammatory mediators are hyper-expressed in melasma skin as endothelin, iNOS, IL17, NF-Kβ, and COX-2, and those are thought to provide an oxidative and inflammatory micro-environment that can lead to chronic pigmentation. Moreover, growth factors as stem cell factor, αMSH, hepatocyte growth factor, b-fibroblast growth factor, nerve growth factor, and VGEF influenced directly melanin production and are expressed prominently in melasma skin (Passeron 2013; Samaka et al. 2014).

The reason why all these alterations occur in melasma but not in adjacent skin that has similar – or even greater – sun exposure regimen throughout life is the key to understand disease pathogenesis and elaborate prevention and management strategies.

Clinical Manifestations

Melasma is characterized by brownish macules with sharp limits and irregular contours. It affects sun-exposed areas, especially the face and neck and less frequently in the arms and sternum (Handel et al. 2014b; Tamega Ade et al. 2013).

According to the clinical distribution, melasma can be classified into centrofacial and peripheral (Fig. 1). The centrofacial lesions are the most common and affect the glabellar region, frontal, zygomatic, nasal, upper lip, and chin. Peripheral melasma occurs at the frontoparietal and temporal regions, preauricular over the mandibular rami (Sheth and Pandya 2011).

In Brazil, centrofacial melasma occurs in 52% of women, but 43% have mixed regions affected (Tamega Ade et al. 2013). In Tunisia, another survey with 188 women disclosed 76% melasma centrofacial and 22% mixed (Guinot et al. 2010).

The exclusively mandibular melasma is rare and may represent a form of poikiloderma of Civatte, because patients are often postmenopausal and analysis of skin biopsies identifies significant actinic damage (Guinot et al. 2010; Mandry Pagan and Sanchez 2000). Studies have shown a low incidence of exclusively peripheral melasma. A Brazilian survey with 302 women has identified only two exclusively mandibular melasma, and 65% of them have also parotideal lesions (Tamega Ade et al. 2013). To reinforce these results, an Indian study disclosed just 1.6% of exclusively mandibular melasma among 312 women (Achar and Rathi 2011).

The most affected site is zygoma, followed by supralabial, frontal, nose, temporal, and chin (Handel et al. 2014a; Tamega Ade et al. 2013).

Although less common, other sites may be involved, such as the forearms and upper arms, neck, back, and sternum, characterizing the melasma extrafacial that can be associated with any of the other facial patterns. Generally, melasma affecting the upper limbs is related to older women, menopause, and use of hormone replacement therapy (O'Brien et al. 1997). Histopathological examination revealed a similar pattern to that described for facial melasma; furthermore there is no epidemiological characteristics that lead to the conclusion that extrafacial melasma composed an independent disease (Ritter et al. 2013).

Diagnostic Tests

The diagnosis is essentially clinical melasma. However, there are some resources to aid the dermatologist in the differential diagnosis.

The Wood's lamp produces a light irradiation with wavelength of 340–400 nm; density and depth of melanin pigment determine the attenuation of fluorescence. The equipment highlights the skin pigmentation difference, and melasma less intense the light of Wood respond better to topical treatments (Ponzio and Cruz 1993).

Under dermatoscopy, the color of melanin depends upon the quantity and level of location, ranging from black when in the *stratum corneum* to brown in the lower layers of the epidermis to the blue or blue-gray in the dermis. The method also allows the identification of vascular lesions in some part of melasma (Stolz et al. 2003; Weismann and Lorentzen 2006).

Histopathologically, melasma is characterized by epidermal hyperpigmentation without increasing the number of melanocytes, but these are hypertrophied and hyperfunctioning with larger dendrites and cytoplasmic organelles, showing high metabolic activity. There is an increased amount of melanin in all layers of the epidermis, an increased number of mature melanosomes. There is a clear damage in collagen IV from basal membrane (*lamina densa*), what leads to a phenomena called pendulous melanocytes (Fig. 2). At the dermis, there is abundant elastosis, and mast cells are the predominant inflammatory cells. The dermal pigmentation does not differ between the skin with melasma and the adjacent healthy skin (Kang et al. 2002; Miot et al. 2010; Shin and Kang 2006; Torres-Alvarez et al. 2011).

The most important differential diagnoses are solar lentigines, toxic melanoderma, Riehl's melanosis, post-inflammatory pigmentation, friction melanosis, ochronosis (endogenous and exogenous), cutaneous lupus erythematosus, actinic lichen planus, acanthosis nigricans, drug-induced pigmentation (e.g., amiodarone), Brocq's erythrosis peribuccalis, periorbital pigmentation, pellagra, café-au-lait macules, facial erythomelanosis follicular, photodermatitis, and Ota's nevus (Kang et al. 2002; Pandya and Guevara 2000; Sheth and Pandya 2011).

These diseases can coexist in patients with melasma; differential diagnosis is important for proper treatment planning.

Impact in the Quality of Life

Melasma is a cause of emotional stress and embarrassment that influences the quality of life of patients. Many report feelings of shame and low self-esteem, affecting your everyday life (Freitag et al. 2008).

MELASQol (Melasma Quality of Life Scale) is a questionnaire that evaluates the effects of melasma in the emotional state, social relationships, and daily activities of patients. This questionnaire consists of ten items, scored 1–7, being the highest score indicative of a poorer quality of life. MELASQol has been validated for different countries, including Brazil (MELASQol-BP) (Balkrishnan et al. 2003; Cestari et al. 2006b).

There is poor correlation between the MELASQol and the severity of the disease estimated by MASI score (Melasma Area and Severity Index), suggesting that the subjective perception of the patient exceeds the dimension of the clinical dyschromia (Cestari et al. 2006a; Freitag et al. 2008).

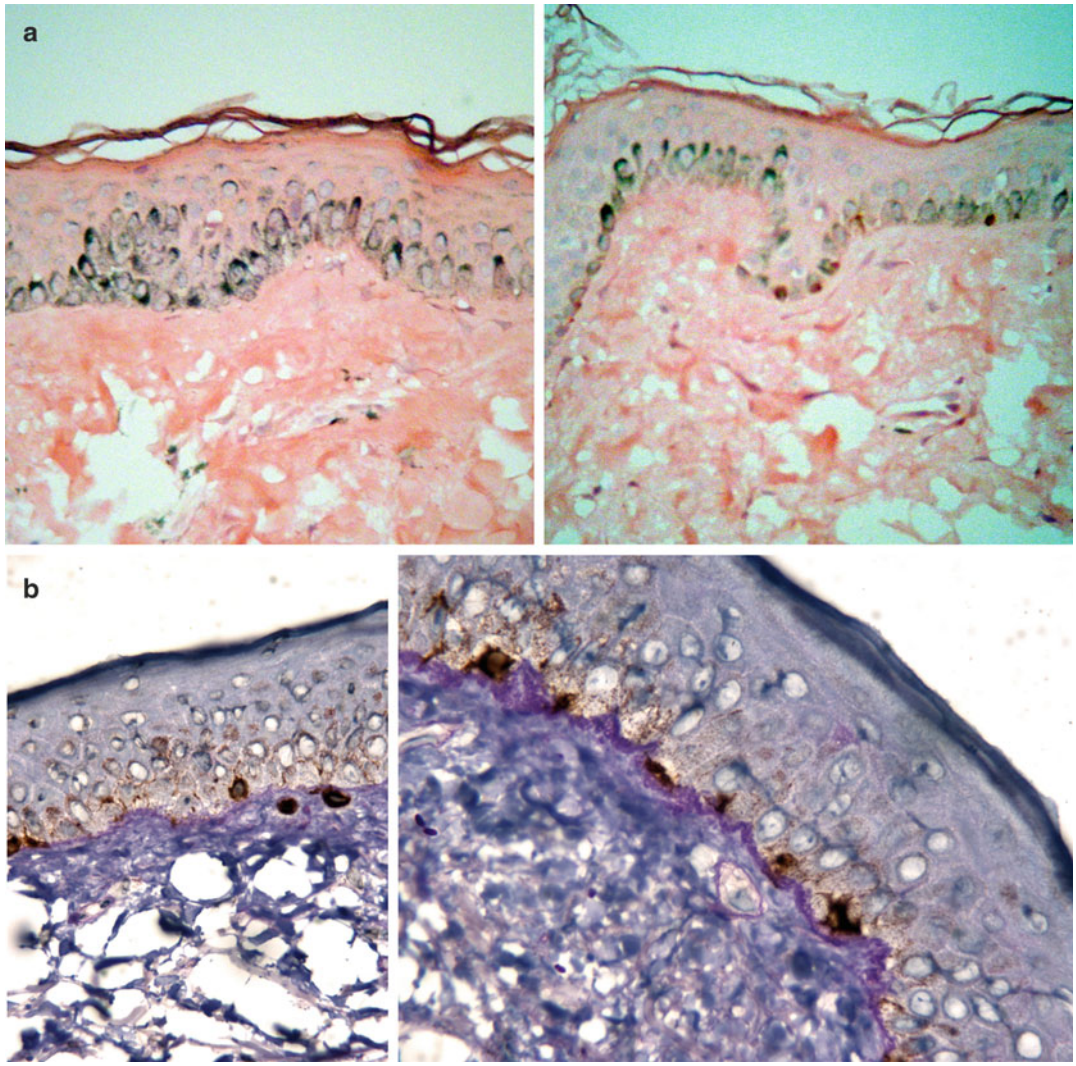

Fig. 2 Histopathology of melasma. (**a**) Fontana-Masson evidenced melanin overproduction in all epidermal layers – 40×. (**b**) Melan-A and PAS showing pendulous melanocytes (into the dermis) and the damage of basement membrane – 100×

MELASQol also reveals that patients with a lower educational level, with moderate depression and anxiety, have a higher degree of emotional impact (Freitag et al. 2008).

Despite melasma not considered a serious disease at a clinical perspective, patients report strong emotional embarrassment and concern. It is necessary to assess individual needs and more satisfactory treatment opportunities facing the individuality of each patient (Freitag et al. 2008; Rendon 2004).

Treatment of Melasma

Best treatment strategy in melasma comprises the recognition of factors of impairment of the lesions as daily sun exposure, phototoxic drugs, cosmetics, skin picking (lead to post-inflammatory pigmentation), adhesion to the treatment, and hormonal steroids (e.g., contraceptive pills or hormone replacement therapy). Efforts should be made for the prompt interruption of these factors.

Preventive measures, as rigorous sun protection and quitting hormonal steroid supplementation, should be indicated to all high-risk patients as pregnant women and first-degree relatives from patients with melasma.

Despite the frequency of the disease, there are still few randomized controlled trials to investigate treatment strategies on melasma. Treatments listed below are – in most part – evidenced by case series with short follow-ups.

To date, there is no curative treatment of melasma. Most strategies lead to the inhibition of tyrosinase, act as anti-inflammatory or antioxidative agents, try to remove pigments from epidermis, and strengthen photoprotection measures. While we do not understand the etiopathogenesis of melasma, treatments are conceived just to minimize its consequences.

Photoprotection

Sunscreens with large wavelength protection (UVA and UVB) are indicated for the prevention and as part of the treatment of melasma (Abarca et al. 1987; Miot and Miot 2009; Rendon 2004). Potent sunscreens (SPF >50 and PPD >20) are recommended to compensate insufficient amount of the substance and lack of periodic reapplication (Schalka et al. 2009).

Despite lack of evidence about the role of visible light in melasma, tinted sunscreens are recommended for women, as warrant more homogeneous spreading. Most studies include longer-wavelength UVA to the analysis of visible light effects, and it can be misleading regarding the positive effect against visible light protection or just larger UVA protection (Castanedo-Cazares et al. 2014; Mahmoud et al. 2010).

Moreover, iron (ferric) oxide, present in most tinted sunscreen, is an important antioxidant compound, and its activity increases as the substance is micronized. Since melanogenesis is an oxidative process and there are an oxidative stress in melasma due to chronic inflammation, the effect of ferric oxide also can be misunderstood as visible light protector but a potent antioxidant (Castanedo-Cazares et al. 2014; Paul et al. 2009; Seckin et al. 2014).

Skin heating due to solar infrared radiation is another factor that can lead to impair melasma lesions. Heat-shock proteins can activate MMP1, MMP3, and MMP9 in the upper dermis that provide degradation of collagen and elastic fibers. To date, there is no sunscreen that effectively blocks infrared radiation, but exposure to heat (e.g., into a car, work in front of ovens) should be avoided (Breathnach 1996).

Physical measures of sun protection (e.g., hat, umbrella, vehicular glass film) and looking for shadows are other recommendations in order to minimize solar incidence in melasma.

Topical Agents

Most topical agents are indicated to tyrosinase inhibition, as anti-inflammatory or topical antioxidants. There are few comparative studies in vivo that evaluate different drugs, concentrations, composition, and tolerability. Main topical strategies on melasma are listed below:

Alpha-arbutin – This is a stable derivative of hydroquinone but less irritating; it blocks the epidermal synthesis of melanin by inhibiting tyrosinase and is more potent than kojic acid. Concentration: 1–6%.

Symwhite – It is a resorcinol derivative and a potent inhibitor of tyrosinase with antioxidant action. Safe, stable, effective, and non-cytotoxic and can be used in eastern skin. Concentration 0.1–0.5%.

Azelaic acid – It is a carboxylic acid synthesized by *Malassezia furfur*, which competes with tyrosinase inhibiting its activity. Its action is also antioxidant, anti-inflammatory, and antibacterial. Concentration: 15–20% in two applications a day (Cestari et al. 2009; Nazzaro-Porro and Passi 1978).

Kojic acid – Derived from *Aspergillus oryzae*, inhibits tyrosinase, induces reduction of eumelanin. Best action when combined with 5% glycolic acid. Concentration: 0.5–6%

(Garcia and Fulton 1996). As an ester (dipalmitate) it increases tyrosinase inhibition.

Tranexamic acid – It blocks melanin synthesis in melanocytes by interfering with the interaction of keratinocytes and melanocytes by inhibiting plasmin-plasminogen system (present in the epidermal basal cells). Concentration: 0.4–3%. Nevertheless, it is more effective when administered orally (see below) (Steiner et al. 2009).

Cysteamine (cloridrato 2-mercaptoethylamine) – Thiol compound that inhibits tyrosinase and peroxidase. Concentration: 5% in cream.

Corticosteroids – Potent corticosteroids decrease melanin synthesis and skin metabolism leading to the improvement of melasma. They can be used alone (e.g., clobetasol 0.05%) or in combination with other agents (e.g., triple association: fluocinolone, tretinoin, and hydroquinone). Skin atrophy, striae distensae, and telangiectasies are the major concern associated with long-term use (Kligman and Willis 1975).

Hydroquinone – It is an aromatic organic compound from the group of the phenols being the most potent blocker of melanin synthesis by inhibiting tyrosinase, preventing the conversion of DOPA to melanin. It is considered the gold standard as depigmentation agent. Concentration 2–4% (higher concentrations are associated with increased incidence of exogenous ochronosis) (Kramer et al. 2000; Rendon et al. 2006; Rendon 2004).

Methimazole – It is an antithyroid medication, potent inhibitor of tyrosinase and peroxidase. Serum levels are not detected if applied in an area up to 50 cm^2. Concentration: 5% (Malek et al. 2013).

Tretinoin – It is a tyrosinase inhibitor retinoid and can also remove pigment granules of keratinocytes and accelerate epidermal turnover. Other retinoids used in melasma include isotretinoin, adapalene, and tazarotene. The association with other agents (e.g., hydroquinone and fluocinolone) improves its effects. Concentration: 0,025–0,05% (Dogra et al. 2002; Griffiths et al. 1993; Gupta et al. 2006; Kimbrough-Green et al. 1994; Leenutaphong et al. 1999; Rendon et al. 2006; Rendon 2004).

Vitamin C – Ascorbic acid inhibits the action of tyrosinase in addition to having antioxidant action; however, their effectiveness is limited by chemical instability. Concentration: 5–20% (Huh et al. 2003; Taylor et al. 2013).

Triple combination and Kligman's formulae – The combination of hydroquinone, tretinoin, and fluocinolone is the first-choice treatment of melasma and characterizes the most potent strategy to improve melasma and long-term maintenance of the results. There are several randomized controlled studies disclosing favorable outcomes for this strategy with sunscreen alone or in combination to chemical peels and tranexamic acid (Arellano et al. 2012; Chan et al. 2008; Godse and Sakhia 2011; Padhi and Pradhan 2015).

Flavonoids, ellagic acid, soya, alpha-lipoic acid, idebenone, phytic acid, and green tea, among others, are used as adjuvants of traditional depigmenting agents (Sarkar et al. 2012b). Nonetheless, there are few controlled studies regarding efficacy and tolerability of these agents in the treatment of melasma.

Oral Agents

Tranexamic acid – Blocks the conversion of plasminogen to plasmin, through the inhibition of the activator of plasminogen, the main protease in epidermis. This results in less free arachidonic acid and a decreased ability to produce prostaglandins that activate tyrosinase. Originally tranexamic acid is prescribed as a pro-thrombotic agent and should be avoided in high-risk patients (e.g., post-thrombotic, smoking, oral hormonal contraceptive, antiphospholipid syndrome) or who need anticoagulation. Oral administration disclosed superior results to topical and intralesional injection for melasma bleaching and should be used as an adjuvant to depigmenting agents as triple association. The usual dosage is 250 mg 12/12 h by 3–6 months. The adverse

effects were uncommon, but reduction of menstrual flow and gastrointestinal discomfort is the most commonly reported (Budamakuntla et al. 2013; Cho et al. 2013; Karn et al. 2012; Li et al. 2014; Na et al. 2013; Padhi and Pradhan 2015; Shin et al. 2013; Wu et al. 2012).

Pycnogenol (*Pinus pinaster*) – It is derived from a French maritime pine rich in flavonoids. It contains potent anti-inflammatory and antioxidant properties. The usual dosage is 75–100 mg/day divided in two to three doses by 2–4 months (Kim et al. 2008; Ni et al. 2002).

Polypodium Leucotomos – It is a tropical bracken native of South and Central America, rich in phenolic derivatives. It has a immunomodulator, antioxidant, and anti-inflammatory properties. The oral administration reduces the sun-induced erythema and pigmentation. These findings indicate it as an adjuvant to topical photoprotection, and also it was shown to reduce pigmentation of melasma. The usual dosage is 250–500 mg/12/12 h by 2–4 months (Ahmed et al. 2013; Middelkamp-Hup et al. 2004; Nestor et al. 2014).

Despite reports of success, there are still few randomized and controlled studies to understand and support the role of oral antioxidants in melasma, neither the comparison of power among them nor different regimens of treatment.

Peelings

Most chemical peels used in the treatment of melasma are aimed to desquamate *stratum corneum* and remove the excess of melanin. They are effective adjuvants in clinical treatment of melasma, accelerating the clinical results (Rendon et al. 2008).

Deeper peelings are matter of concern in melasma since the inflammatory process can lead to melasma rebound and post-inflammatory hyperpigmentation.

Glycolic acid – alpha-hydroxy acid derivate from sugar cane. Peelings should be performed each 2–4 weeks. Concentration: 30–70% (Godse and Sakhia 2011; Hurley et al. 2002; Ilknur et al. 2010; Lim and Tham 1997; Sardana et al. 2013; Sarkar et al. 2002, 2012a).

Jessner's solution – Combination of resorcinol (14%), salicylic acid (14%), and lactic acid (14%). There are several reports of its efficacy in the treatment of melasma as adjuvant to clinical therapy (Ejaz et al. 2008; Lawrence et al. 1997; Sarkar et al. 2012a; Sharquie et al. 2006).

Tretinoin peel – as effective as Jessner's solution or glycolic peel 70% in the treatment of melasma. Concentration: 1–5% (Khunger et al. 2004).

Salicylic acid – as effective as Jessner's solution in the treatment of melasma, especially among darker patients. Concentration: 30% (Ejaz et al. 2008).

Trichloroacetic acid (10–30%) and lactic acid (92%, pH 3.5) are reported as effective in the adjuvant treatment of melanoma but did not accumulate evidence that proves them superior to the previous peelings (Nanda et al. 2004; Sharquie et al. 2006).

Light-Related Technologies

Most light technologies involve lasers and intense pulsed light; nevertheless there are several equipments and regimens of use (e.g., fluence, filters, pulse duration, energy, and wavelength) that difficult the comparison of the results among them as well as the reproducibility of the outcomes.

Intense pulsed light (IPL) – It is a non-coherent light source, with filters between 500 and 1,200 nm. IPL has affinity for melanin and hemoglobin. There are over 20 different types of IPL equipment in the world, but commonly filters of 500–550 nm are the most reported in the treatment of melasma. It is an alternative for those patients refractory to other treatments. Care should be taken to not trigger the rebound phenomenon or provoke post-inflammatory hyperpigmentation due to epidermal injury. The different studies have shown its effectiveness if simultaneously employed in clinical treatment with bleachers but did not undergo long-term

follow-up (>1 year). In addition, there are reports of facial melasma aroused after IPL for photoaging, warning that the epidermal heating can trigger subclinical melasma. In patients with important vascular component, IPL can contribute in this specific treatment (Chan and Kono 2004; Chung et al. 2014; Moreno Arias and Ferrando 2001; Na et al. 2012; Negishi et al. 2004; Wang et al. 2004; Zaleski et al. 2012; Zoccali et al. 2010).

LASERS – The use of laser for treatment of pigmentary disorders is based on the theory of selective photothermolysis, which proposes a specific spectrum of light emitted by a specific laser that is selectively absorbed by a cell type or tissue. Short and selective pulses to selective pigments can cause physical damage to the pigmentary structures (Goldberg 1997). Similar to the chemical peeling, lasers have an increased risk of side effects by direct damage to the skin, which becomes more prevalent in patients with higher phototype. The following technologies have achieved some benefits in the treatment of melasma.

Nonablative fractional laser – Erbium 1,550 nm. It provides a melanin and melanocyte reduction in melasma. Best results are obtained in fair skin patients after four monthly sessions. There is up to 20% of improvement, but the relapses are very common along the time (65%) (Goldberg et al. 2008; Lee et al. 2009; Naito 2007).

Nonablative fractional laser – Thulium 1,927 nm. This wavelength has a higher water affinity than the 1,550 nm, providing less epidermal injury (Ho et al. 2013; Polder and Bruce 2012).

Q-switched neodymium-doped yttrium aluminum garnet (QS-Nd:YAG −1,064 nm) – It has a best affinity for the melanin than the previous lasers. As adjuvant to photoprotection and topical bleachings, five sessions (low fluence) weekly can reduce melasma pigmentation. The main concern resides in post-inflammatory hyperpigmentation or hypochromia due to epidermal injury and relapse of melasma in 12 weeks in all patients (Park et al. 2011; Wattanakrai et al. 2010).

Pulsed dye laser (PDL) – This is a laser with high affinity for hemoglobin and indicated for the treatment of vascular component of melasma. The use of up to three applications every 4 weeks, concurrently with the depigmenting clinical therapy, promotes improvement of melasma that was maintained for more than 8 weeks (Passeron et al. 2011).

Ablative fractional laser – CO2 10,600 nm. Ablative fractional lasers at high risk of post-inflammatory hyperpigmentation and low level of tolerance due to the intense epidermal damage. However, low-fluence fractional laser evidenced to be an adjuvant to clinical treatment of melasma, promoting higher depigmentation than clinical treatment alone (Rivas and Pandya 2013; Trelles et al. 2010).

Other Surgical Procedures

Dermabrasion – Since melasma does not develop on scars, superficial (upper dermis) dermabrasion was considered a curative technique for melasma.

There is just one case series with 398 Thai patients and long-term follow-up (5 years) and the report of high rates of maintained success (Kunachak et al. 2001).

By the way, microdermabrasion was proven to be of minimal benefits in the treatment of melasma; it favors the penetration of agents and peelings (e.g., trichloroacetic acid 15%) (Bhalla and Thami 2006; Cotellessa et al. 2003; Lee et al. 2003).

Microneedling – Microneedling is a technique of repeated drilling of the dermis in order to induce repair and neocollagenesis. Recently, microneedling has been used to enhance transdermal absorption of drugs (drug delivery) (Doddaballapur 2009; Lee et al. 2014; Yoon et al. 2010).

The most widely used instrument to perform this technique consists of a polyethylene roll full of sterile stainless steel needles symmetrically aligned in rows for a total of 190 units on average, varying according to the manufacturer. The length

of the needles may vary from 0.25 to 2.5 mm according to the model. Topical local anesthetics should be used, and, sometimes, association with anesthetics blocks is necessary (more than 1 mm needles) (de Andrade Lima et al. 2013; Fabbrocini et al. 2009, 2011).

A comparative study of microinjections of tranexamic acid against microneedling associated with the topic tranexamic acid in melasma extrafacial was performed. The group associated with the microneedling showed superior improvement in MASI (44.4%) (Budamakuntla et al. 2013). Another study evaluated 20 patients using depigmentation serum isolated on a hemiface against microneedling associated with depigmentation serum in the other hemiface. The hand treated with the combination therapy showed a statistically reduced MASI, in addition to a clinically important improvement (Fabbrocini et al. 2011).

There are anecdotal reports that the isolated microneedling has lightening melasma. In fact, the repair of the upper dermis and collagen synthesis-induced microneedling have the potential to reverse the damage of the dermal melasma. Controlled studies should be performed to understand the role of microneedling (alone or as a means of drug delivery) in the treatment of melasma.

Prognosis

Melasma is a chronic and relapsing disease despite adequate treatment. In general, treatment response is better among fair skin patients, younger than 35 years or older than 45 years old (Zaleski et al. 2012).

The more prominent the pigmentation, and the more extensive the disease, the less effective the treatment response and more common the relapses, principally after sun exposure or skin injury (e.g., peelings and IPL) (Sarkar et al. 2012a).

Melasma tends to fade spontaneously after menopause and with aging, probably due to the decrease of hormones and gradual loss of melanocyte number and function in the epidermis.

Take-Home Messages

1. Melasma is a chronic and acquired localized hypermelanosis, which affects mainly women of intermediate phototypes during fertile age.
2. Sun exposure is the main risk factor for melasma, exerting role both in it appearance as in worsening and maintenance.
3. The exact mechanism of skin melanogenesis in melasma is currently not well understood.
4. The upper dermis and lamina densa damage suggest the role of dermal injury/repair process in disease pathogenesis.
5. Regular application of broad spectrum and physical sunscreen as well as avoidance of ultraviolet and visible light are important for preventing recurrence.
6. Topical bleaching agents are still first line treatments for melasma.
7. Microneedling is a promising treatment modality for melasma.

Cross-References

- ▶ Approach in Photodamaged Skin, Melasma, Acne, and Rosacea
- ▶ Chemical and Physical Sunscreens
- ▶ Cleansers
- ▶ Cosmeceutical Ingredients: Botanical and Non-botanical Sources
- ▶ Hydroxy Acids
- ▶ Nutraceuticals in Dermatology
- ▶ Oral Photoprotection
- ▶ Photoprotection: Concept, Classification, and Mechanism of Action
- ▶ Retinoids
- ▶ Vitamins and Other Antioxidants

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Cosmetic Approach for Healthy and Damaged Hair

Antonella Tosti, Alessandra Juliano, Leila David Bloch, and Miguel Canales

Abstract

The word hair usually refers to two distinct structures, hair follicle, the part locates in the dermis, and the hair shaft, which is the hard filamentous part that extends above the skin surface and varies with ethnicity in diameter and format. The hair shaft can be modified with different cosmetic procedures and also can be damage during the process. This chapter will approach hair anatomy, structure of hair shaft, hair damage, hair analyses, and different ways to process hair changes.

Keywords

Hair shaft • Hair shaft damage • Hair treatments • Hair cuticle • Hair medulla • Cortex • Cuticle • Keratin

Contents

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Introduction

Throughout history, hair has played a significant role in our society – it is associated with youthfulness and beauty in women and virility and masculinity in men; so it is no surprise that hair loss and hair damage can make many men and women feel self-conscious.

Human hair functions as a means of regulating body temperature, and it acts as a sensory organ. Hair also helps to protect the skin from external damage such as sun, wind, and foreign particles. The structure of hair is comprised of two main parts: the follicle and the hair shaft. Hair shafts are the visible part of hair on the surface of the skin and can have different formats according to the race. The hair shaft can be modified by thermal and chemist process, but some of the changes can cause hair shaft damages that can be seen under hair dermoscopy and high technic methods for assessment of hair damage and hair repair (Vogt et al. 2008).

Normal Hair

Structure of the Hair Shaft

Human skin contains approximately 5 million of hair follicles, with 100,000 being located on the scalp. The quantity of hair varies according to ethnicity (Table 1).

The structure of hair is comprised of two main parts: the follicle and the hair shaft. The hair shaft, the part of the follicle that emerges through the skin, exhibits no biochemical activity and is considered "dead." It is made up of proteins, lipids, water, melanin, and trace elements. A transverse cut across the hair shaft reveals that there are three principle layers: the medulla, the cortex, and the cuticle (Vogt et al. 2008).

Table 1 Number of hairs on the scalp by ethnicity

Caucasian	90,000 a 13,000
Black	90,000
Asian	90,000

The Medulla

The central part of the medulla, whose function is unknown, contains polygon-shaped cells and has a spongelike characteristic. In the terminal hairs generated during infancy, the medulla can be absent or fragmented, while the medulla is always absent (Vogt et al. 2008).

The Cortex

Surrounding the hair medulla, the cortex represents the bulk of the hair fiber mass. The cortex is composed of keratinized fibrous cells arranged longitudinally, and, when completely matured, they are wrapped in cysteine-rich keratin filaments. The cysteine forms strong covalent disulfide bonds contributing to the form, stability, and texture of hair. Disulfide bonds remain intact when the hair is wet, allowing the hair to return to its original appearance once dried. Other weaker bonds, such as van der Waals, hydrogen bonds and ionic bonds broke when hair is wet. Melanocytes, which determine the color of the hair fiber, are present in the cortex. The melanocytes have granules of eumelanin (brown and black) and/or pheomelanin (yellow and red) with various compositions and densities, enabling a wide spectrum of hair colors (Vogt et al. 2008; Sinclair et al. 1999; Osorio and Tosti 2011).

The cortex is composed of three fundamental structures, so that the properties of the cortex are maintained: the macrofibers, microfibers, and protofibers. Each cortical cell contains five to eight macrofibers with a low quantity of sulfur. Macrofibers are elongated structures made up of microfibrils. Each macrofiber contains 8–11 microfibers, with an intermediate level of sulfur. Microfibers contain protofibers with high

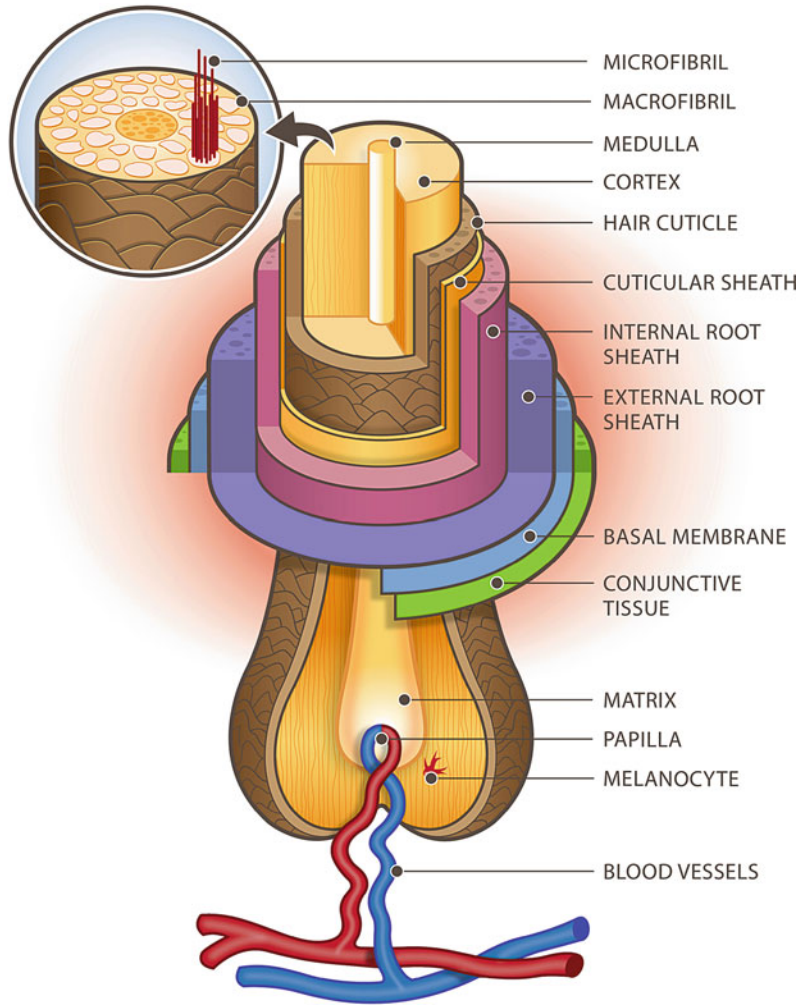

Fig. 1 Hair follicle anatomy

concentration of sulfur. The protofibers are formed by four chains of interlaced keratin fibers, known as alpha-helix, which is a fundamental unit of the hair shaft (Fig. 1).

The Cuticle

The cuticle is the outermost layer of the hair shaft. It contains long dead flattened cells (e.g., flakes) arranged like tiles. They can form five to ten layers, each one between 350 and 450 nm of thickness. It is a very thin and translucent, allowing visualization of the cortical pigments. The cellular structure of the cuticle contains three layers: a cysteine-rich layer called layer A, the exocuticle, and the endocuticle. The outer surface is composed of branched fatty acids with hydrophobic properties, the so-called f layer, which is very important for the development of hair treatment products. Between the cortical cells and the cuticle cells, there is a complex cell membrane that has an adhesive quality and provides protection to the cortex (Osorio and Tosti 2011; Rossi et al. 2003)

Keratins

The hair shaft is made up of keratins, which are protein filaments with an alpha-helix central structure and a spiral shape. The keratin can be grouped

Table 2 Hair shaft diameters according to race and ethnicities

Type	Hair shaft diameter (μm)
Caucasian – blond hair	40–80
Caucasian – medium brown/ black	50–90
Caucasian – redhead	50–90
Black	60–100
Asian	80–120

into intermediate filaments type 1 (acid) and type 2 (basic to neutral). There are 11 type 1 keratins for hair and 6 type II keratins for hair (Robbins 1988; Draelos 2010; McMichael 2003; Lindelof et al. 1988).

The bonds within the chemical components of the keratin can have varying degrees of strength (e.g., disulfide bonds, hydrogen bonds, ionic bonds) conferring firmness, rigidity, and flexibility of the hair. When these chemical bonds are permanently or temporarily broken, they shape and form of the hair can change (Robbins 1988).

Types of Hair

The majority of hair characteristics, such as hair diameter and hair structure, are genetically programmed. The structure of the hair shaft and also the chemical composition are similar between Caucasians, Asians, and Africans. But, there are important differences between mechanical properties and geometry of the hair (McMichael 2003).

The shape of the hair shaft is partially determined by the hair follicle. One of the principle determinants of the hair shaft shape is the location of the hair bulb, the size and the shape of the dermal papilla, and the curvature of the hair follicle along its length. This determines the diameter, the longitudinal shape, and the curliness of the hair in each individual. Environmental factors and external factors however, such as chemical treatments or friction, can change the natural shape of the hair fiber (McMichael 2003).

Hair shaft diameter varies with ethnicity (Table 2) and also the hair shape. Caucasians have hair with an elliptical cross-sectional, cons, and the hair shape can be straight or wavy (Fig. 2).

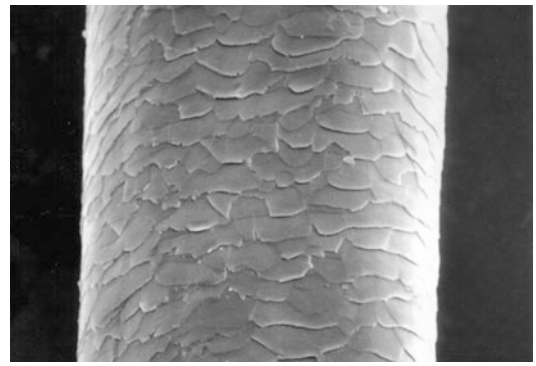

Fig. 2 Normal shaft (Courtesy of L` Oreal)

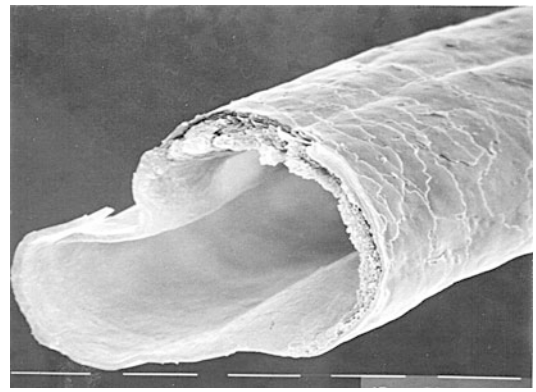

Fig. 3 Electronic scanning microscope image – African (elliptical)

Asian hair has a round cross-sectional shape consistent with straight hair. In comparison, the African hair has a cross-sectional shape that is elliptical or flattened (Fig. 3).

When the hair is wet due to water, it hair can stretch up to 30% longer than its usual length, without suffering any damage. The African hair has a lower absorption of water due to a different chemical composition of the hair fiber, especially the lipids.

The degree to which hair is wavy is directly related with the characteristics and structure of the shaft (Fig. 4). This also determines how easily it can be styled (i.e., combed, dried, reshaped). African hair has a high degree of friction when styling resulting in major potential for hair shaft damage.

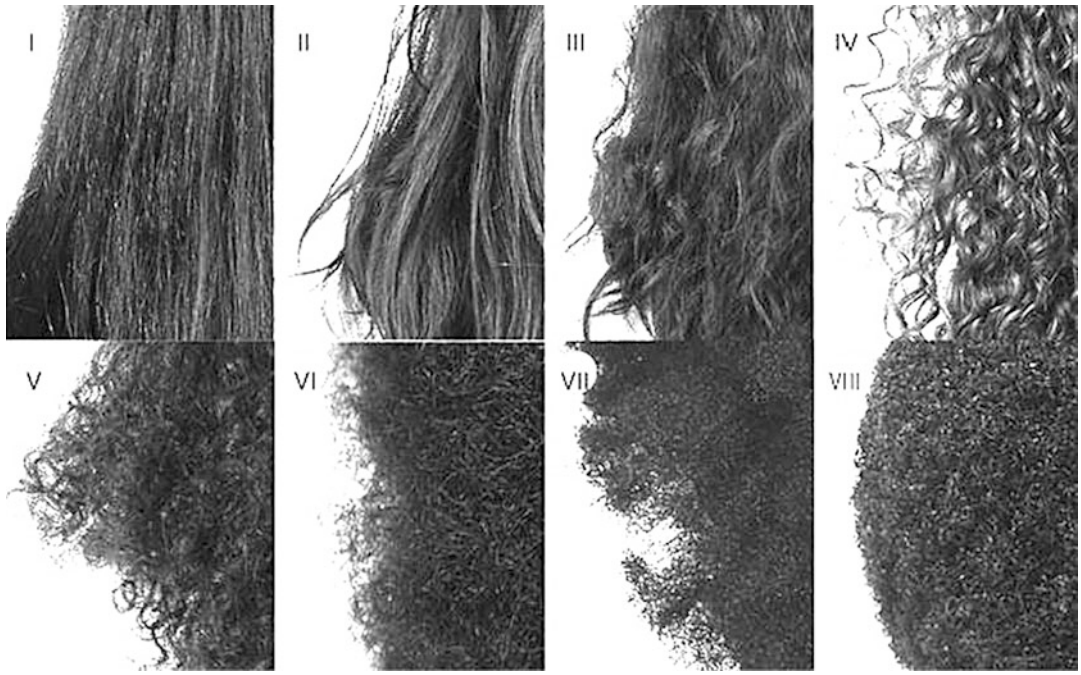

Fig. 4 Hair classifications according to curl (Courtesy of L` Oreal)

The texture of the hair also influences hair shiness and the ability of sebum to coat the hair shaft. Straight hair allows the sebum to coat it from the root to the shaft. The curly irregular surface of African hair makes it difficult for the sebum to coat the hair, despite the large quantity of sebum produced. As a result, the hair has a more opaque appearance and is less shiny (Table 3).

When exposed to hair-straightening products, African hair breaks easier. The fragility can be explained by natural constrictions along the length of the fiber, by the helical shape of the fibers, and by the presence of micro-fractures/fractures along the shaft (McMichael 2003).

The hair shafts in Asians are round, thick, and straight. Asian hair is difficult to perm and dye, requiring higher concentrations of chemical treatments and longer exposure time to the chemicals. This can frequently damage the hair fiber.

Gray hair, independent of race and ethnicity, is coarse and rigid and dries quicker than pigmented hairs, although there are no chemical differences in the fibers.

The desire for straight hair is attributed to a model of beauty and social status that appears to be universal. The search for this model results in the transformation of the natural shape of hair. This shape, as previously mentioned, is connected to the shape of the hair follicle. Wavy hair has an

Table 3 Hair shaft characteristics according to race and ethnicities

	Asian	Caucasian	Black
Format	Straight	Straight, waive, elliptic	Curly, spiral
Transversal cut	Round	Round and oval	Elliptic, irregular, flat
Pigment	Rich in eumelanin	Mixed of eumelanin and pheomelanin	Rich in eumelanin
Comb	Easy	Vary	Hard
Sebum/fat	High	Medium	Low
Hydration	High	Medium	Low
Tensile strength	High	Medium	Low
Proportion cuticle × cortex	Low	Medium	High

asymmetric expression of keratin proteins, and the hair follicle is curved. It is possible, through chemical treatment, to straighten the hair or to make hair curly. Temporary changes in hair texture and shape occur when the hydrogen bonds or ionic bonds are altered. A more permanent result requires modification of the covalent bonds, for example, breakage and restructuring of the disulfide bonds (Draelos 2010).

Hair damage usually occurs due to aggressive mechanical manipulation, exposure to high temperatures, and the incorrect application of chemical products.

Chemical and Thermal Modification of Hair Structure

Thermal Modification

The processes to modify the hair shaft using thermal energy have been used since ancient Egypt. Even today, thermal styling is the most utilized way to modify the characteristics of the hair shaft. Method became more practical since 1920 due to portable hair dryers and more recently due to the commercialization of hair irons (Lindelof et al. 1988).

The mechanism of action involves the basic rearrangement of hydrogen bonds in the hair shaft due to the high temperature and the mechanical stress. The hair shaft first has to be moist to enable the breakage of hydrogen bonds in the process of keratin hydrolysis. This technique allows the temporary relaxation of the hair curl. This process makes the hair straight. Fast dehydration with the hair dryer maintains the straightness of the hair. Applying a hot hair iron shapes the cuticle cells in a way that is flat and parallel to the hair shaft. The hair shaft becomes more straight and shiny due to the more efficient reflection of light (Wortmann et al. 2007; Lee et al. 2011; Wortmann and Deutz 1993).

Thermal hair straightening is a temporary method because the hair shaft will return to its normal shape once exposed to humidity or water. But it can cause permanent hair damage due to denaturation of the hair shaft proteins with high temperatures. The integrity of the hair shaft is threatened with temperatures that are between 235 °C and 250 °C in dry hair and 155–160 °C in moist hair (Wortmann and Deutz 1993).

The temperature of some devices exceeds these limits. Care must be taken to avoid repeated exposure to high temperatures.

The hair iron became more popular when the temperatures were maintained more constant. Additionally, improvements in hair iron coatings such as ceramic or titanium cause less friction and increase the durability of the straightening effect. The reduction of friction is fundamental because it maintains the surface of the cuticles more regular and flat, reducing the chance of fracturing the hair during the process (Wortmann and Deutz 1993).

The hair breakage due to the use of hair dryers was studied in Korea. This study showed that keeping the hair dryer at 15 cm of distance from the hair with continuous movements caused less damage than drying the hair at room temperature (Thibaut et al. 2005).

Chemical Modifications

The process of chemical modification of the hair shaft is considered more durable and varies according to the type of hair-straightening product that is used. There are four kinds of hair products commonly used to straighten the hair: (1) thiols, (2) bisulfate, (3) hydroxides, and (4) formaldehydes.

Thiols

The thiols include chemical agents based on thioglycolate, ammonia, and ethanolamine. These products can be used to straighten the hair or make it more wavy, a process that is usually referred as “permanent” (Zviak and Sabbagh 2008).

The compounds used for hair straightening are usually supplied in the form of creams, whereas agents used to make the hair curly (“permanents”) are usually lotions.

The thiol straighteners can leave behind some waviness in the hair types of V–VIII, falling short of the desired result. This type of chemical process

results in hair shaft dehydration, which can be reduced by adding glycerin in the formula.

Straightening involves two phases. First, the disulfate bonds of the cysteine amino acids are cleaved (reduction), which promotes the swelling of the keratin. This makes the hair malleable to be straightened or curled. In the second phase, the bonds are rebuilt (oxidation).

In the majority of the cases, a thiol concentration of 7.5% is used with a pH range of 9–9.3, depending on the type of the hair.

These products can be used in dyed hair and hair with previous permanents, but it is not recommended for light hair or hair that has been previously treated with hydroxide products, which can cause a chemical breakage of the hair shaft. Hair dye can be applied after 15 days of the straightening process. Hair that has undergone permanent treatments must not undergo a straightening treatment and vice versa. Hair must grow again prior to applying another chemical treatment that alters the shape of the hair (Thibaut et al. 2005; Zviak and Sabbagh 2008).

A new technique that is becoming popular in Brazil and Japan, which is known as "chocolate brushes," Francesa, and others, is characterized by heating the hair shaft prior to the oxidation phase of the thiol treatment.

After some time, the process has to be repeated only in the hair that has grown. Treatment must be avoided in the hair that has a previously been treated. The recommendation is to wait a minimum of 6 weeks, depending on the amount of new hair growth (Cannell 1988; Khumalo et al. 2010).

Bisulfite

Even though used for decades, bisulfite treatments are now less utilized than hydroxide treatments, because it is less effective in hair that is very wavy. Its effectiveness on the disulfide bonds depends on the pH of the solution, but sulfates are not very stable in the acidic pH ranges. Commercial products have a pH varying between 6.7 and 7.0. With the pH 7, 15% of the residual cysteine is reduced.

The first phase of the reaction involves the reduction of the cysteine via a nucleophilic reaction. To keep the hair in the shape that is desired, a neutralizing solution must be used. For example, a common neutralizing solution is carbonate or sodium bicarbonate.

Hydroxides

Initially used as home formulations in the 1930s, the commercial use dates back to the 1950s. Hydroxides are most commonly used in African hair. In this era, the formulations were very irritating to the scalp, and use was restricted to the professionals. Application of petrolatum was needed to protect the scalp. In the 1970s, the formulations became less caustic prompting their commercialization (Cannell 1988).

The hydroxides are alkaline creams divided into two major types: caustics (sodium hydroxide) and non-caustic (guanidine, lithium, and potassium). The concentrations used range from 5% to 10%, and the pH varies between pH10 and pH14, with the sodium and lithium being more potent and the guanidine hydroxide less potent but still causing hair damage (Cannell 1988).

The mechanism of action consists of substituting approximately 35% of the cysteine amino acids to lanthionine. This occurs through the cleavage of disulfide bonds, with the loss of a sulfur atom, which transforms hair into a straight new shape. Then the disulfide bonds are reconstituted. For this the hydroxide solution must be washed away, and then neutralized with acidic agents such as hydrogen peroxide and sodium bromide. There is compatibility amongst the different hydroxides, but a test should be done on a lock of hair prior to treating (Shansky 1963; Cannell 1988).

Cross-Linking Keratin Treatments

Brazilian Keratin Treatment

The composition used is a base solution of formaldehyde (formal) 37% mixed with liquid keratin and a cream conditioner, which must be applied on the hair shaft, followed by the use of a hair drying method such as a blow dryer or hair iron (Cannell 1988).

The formaldehyde bonds to the keratin proteins of both the cuticle and cortex, and the amino acids of the keratin solution are hydrolyzed, stiffening the hair along its length. The

result is a rigid hair shaft with intense shine. The hair shaft can become susceptible to fracture due to the everyday traumas such as brushing the hair and mechanical manipulation (e.g., tying the hair in pony-tails, etc.) (Wortmann et al. 2007; Cannell 1988).

This process creates a health hazard as the heat applied to the hair causes the formaldehyde to evaporate with possible risk of inhalation. This can cause health risks to the professional applying the treatment and the client.

Other Similar Hair Keratin Treatments

- *Progressive*: composed of 0.2% formal, hydrolyzed keratin and emollients. The duration of the effect is 1–3 months and between 30 and 40 washes.
- *Marroquina:* composed of clay and 0.2% formol. The duration of the effect is 3–5 months.
- *Chocolate:* composed of theobromine, liquid keratin, and silk protein and cacao extract and caffeine. Duration of the effect is 2 months.
- *Francesa:* composed of ammonium thioglycolate and keratin. Duration of effect is 4 months.
- *Definitive* (*japonesa*): indicated for hair that is already straight or slightly wavy. Duration of effect is 4–6 months.
- *Progressive without formal:* composed of ammonium thioglycolate. Duration of the effect is 4 months.

The Application Process of Hair Products

The first hair relaxation treatment must be applied all along the hair shaft, and the subsequent treatments must be only applied to the areas of new hair growth. The intervals between treatments vary between 6 and 8 weeks depending on the rate of hair growth, which can vary between 4 and 18 mm/month (Cannell 1988).

There are different factors that should be taken into account when choosing the right product for treatment such as diameter of the hair, waviness of the hair, and porosity and the type of treatment previously applied (McMichael 2003).

Hair damage can occur if the interval between treatments is short, if the exposure time is too long, and if there is improper neutralization of the relaxer (McMichael 2003).

The neutralization is a fundamental part of the process to reestablish the pH of the hair shaft. High pH solutions can cause the hair shaft to swell by 70–80%, which may lead to hair damage (Cannell 1988).

Effects

The incompatibility between the hydroxides and the thiol families is due to the way they affect the sulfur bonds. The hydroxides transform the hair fiber by removing a sulfur atom, a process known as lanthionization. The thiol families do not remove a sulfur atom but reorganize the bonds in a different configuration. Both of these mechanisms are irreversible and determine their incompatibility (Shansky 1963).

Hair damage is usually due to aggressive mechanical manipulation, exposure to excessive high temperatures, and the incorrect use of chemical treatments. Note that caustic products are more irritating to the scalp and the non-caustic products can change the quality of the hair shaft (Shansky 1963).

Products with high pH can cause swelling of the hair fiber, cuticle abrasion, loss of hydrophobic lipid layer of the cuticle, increased cuticle porosity, reduction of the traction resistance, and increase the plasticity. These alterations in hair fiber quality can cause crack and erosions of the cuticle.

Possible side effects noted after hair treatments include scalp burning, fracture of the hair shaft, cicatricial alopecia, follicular degeneration syndrome, telogen effluvium, and damage to the pilosebaceous unit (Cannell 1988).

Treatments that moisturize the hair after chemical treatments can improve the quality of the hair. A good moisturizer can make combing or brushing the hair easier reducing the frizz and protecting the surface of the hair (Draelos 2008).

Hair Dyes

Hair dyes are usually classified by the durability of the color: gradual, temporary, semipermanent, and permanent. The pigments can be natural or

synthetic dyes. The most often used natural hair dye is henna, but it can generate a wide variety of color tones (Wortmann et al. 2007; Lee et al. 2011).

Gradual Dyes

These dyes are composed of different metals such as lead, silver, and bismuth. The results of the gradual dyes are limited to black, dark brown, and gray tones. They are used to darken the natural color of the hair.

The metal particles react with the cysteine contained within the cuticle, to form a metal sulfide, which will be deposited in the hair shaft and will generate a gradual pigmentation (Lee et al. 2011).

Men most often use this method. The application can take approximately 5 min. The disadvantages to this treatment are the poor smell of sulfur due to the chemical reaction and its irreversibility. It also does not permit other forms of hair dying because of the risk of hair breakage.

Temporary Dyes

These dyes are usually composed of water-based solutions and are of a high molecular weight, which prevents from penetrating the cuticle. The dye is usually lost after the first hair wash. In some instances, the dye is able to penetrate the cuticle and remain longer, for example, if the hair underwent a prior treatment that increased the porosity of the cuticle. These dyes usually come in the form of sprays, mousses, shampoos, and gels (Lee et al. 2011).

Semipermanent Dyes

These dyes are usually consist of synthetic hennas free of ammonia and derived from coal tar of low molecular weight (diamines, aminophenols, phenols). It contains a monoethanolamine molecule (MEA), less potent but also less oxidative. The dye diffuses into the cortex and can have a duration of 4–6 weeks or eight hair washes with shampoo. The dyes can darken the hair into three different tones. It can cause less hair damage, but the results are unpredictable in hair that has previous chemical treatments. It is usually applied when the hair is moist or wet and takes about 40 min after which the product must be washed away. In damaged hair, products with varying molecular weights must be used to maintain the uniformity of colors (Lee et al. 2011).

Permanent Dyes

Permanent dyes consist of an oxidation process which utilize alkaline solutions (ph 9–10) which has an ammonium base which penetrates the cuticle and can reach the cortex. It can lighten the hair or make the hair darker. It is the most efficient way to dye gray and white hair.

The permanent dye is a result of oxidative reactions between the para-aminophenols and meta-aminophenols and phenylenediamines and hydrogen peroxides. The pigment is not removed with hair washes (Wortmann and Deutz 1993).

If the objective is to reach a lighter tone, it is first necessary to depigment the hair with an ammonia persulfate, potassium, and hydrogen peroxide. The final pigment must be applied in the depigmented hair. The hair roots must be re-dyed every 4–6 weeks, and any hair relaxer treatments should be done 2 weeks prior to the hair dying (Lee et al. 2011).

Lightening the Hair Color

This is a process of partially or totally removing the melanin in the hair shaft. The most common method utilizes hydrogen peroxide 12% in an alkaline base such as ammonia. The mechanism of action is not well understood. Two phases are involved. The first phase is to break the bonds between the pigment particles. The second phase involves the breaking of the melanin structure. This process is time dependent and difficult to control. An exposure time of 1–2 h can destroy some of the disulfide bonds and cause cuticle damage, leaving the hair shaft more porous and compromised (Lee et al. 2011).

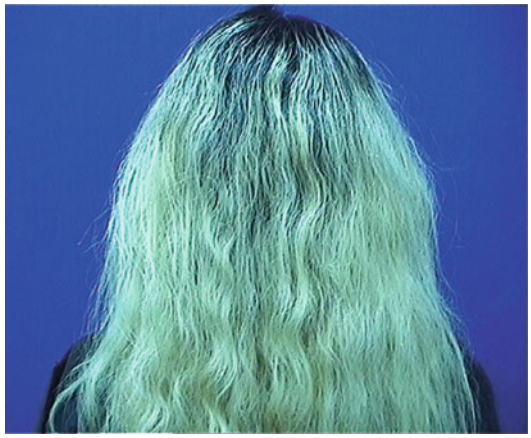

Fig. 5 Hair shaft damage – trichorrhexis nodosa

Fig. 6 Trichorrhexis nodosa – dermoscopy 20× magnification

Fig. 7 Trichorrhexis nodosa – dermoscopy 50× magnification

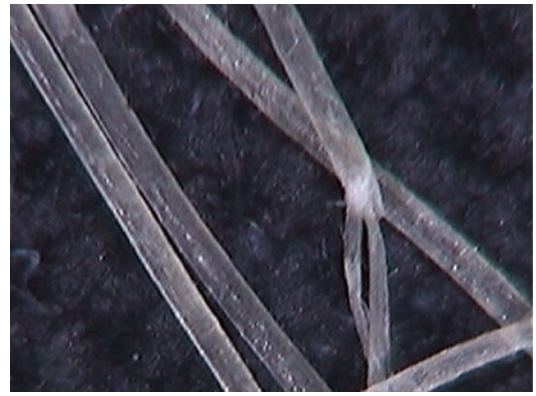

Fig. 8 Trichoptilosis – dermoscopy 70× magnification

Damage Hair

Trichorrhexis Nodosa

Trichorrhexis (TN) nodosa (Fig. 5) describes a nodular swelling where the hair shaft breaks into numerous fibers. It can have different appearance depending on magnification and severity. The nodules represent a focal fracture of the cortical fibers that were pushed out and exposed due to the rupture of the cuticle. Before complete breakage, the affected area appears like opposing two white brushes. Causes of TN include mechanical, thermal, and chemical traumas (Gama 2010).

The typical clinical presentation is the presence of white and/or gray small spots along the hair shaft. The affected hairs are susceptible to hair fracture and severe TN can cause patches of alopecia.

Trichorrhexis nodosa (Figs. 6 and 7) is often associated with other signs of hair shaft damage including trichoptilosis and trichoschisis that can be found in the same hair shaft.

Trichoptilosis

This term describes a division of the tip of the hair shaft (Figs. 8 and 9), most commonly known has "split ends." This is common in damaged hair, especially in long hair. Central trichoptilosis is common in African hair (Gama 2010).

Fig. 9 Trichoptilosis – dermoscopy 70× magnification

Fig. 10 Trichoschisis – dermoscopy 70× magnification

Fig. 11 Hair dermoscopy: residues in hair 50× magnification

Fig. 12 Hair dermoscopy: residues in hair 70× magnification

Trichoschisis

This term describes a transverse fracture of the hair shaft, which is also known as "greenstick fracture" (Fig. 10; Gama 2010).

Bubble Hair

This term describes the presence irregular bubbles inside the cortex of the hair shaft. This finding is visible at dermoscopy or using electron microscope techniques. This abnormality is due to application of very high temperatures with hair dryers, hair irons, and hair curlers on wet hair. This causes acute evaporation of the water with bubble formation within the cortex. It can cause rupture of the hair shaft (Wortmann et al. 2007; Lee et al. 2011; Draelos 2008).

Residues in the Hair

Residues in the hair (Figs. 11 and 12) can be confused with hair disorders or parasitosis.

Trichonodosis

This is the formation of single or double knots in the hair shaft. The cause is due to trauma especially during hair brushing and styling or friction

due to rubber bands or contact with the pillow. This pathology causes twisted hair and hair breakage. It is common in people with thin hair, particularly in the nape. It is also very common in African hair (Wortmann and Deutz 1993).

Methodologies for Hair Damage and Hair Repair Assessment

The hair fiber may present several levels of structural damage, causing it to become fragile, dry, and rough, without gloss. Solar radiation, hair dyes, bleaching, straighteners, high temperature, washing, and brushing, among other factors, promote damage. These factors alter hair mechanical properties as well as its surface (cuticle). Therefore, it is important to be able to quantify and understand the levels of hair fiber damage to enable the development of effective cosmetic formulations.

Below is a list of the most used and important methods concerning hair damage repair assessment and quantification.

Protein Loss Assessment

The quantification of protein loss in damage-exposed hair as well as its reduction by cosmetic treatments may be performed by UV-visible spectrophotometric methods. The most widely used are Lowry et al. (1951), Bradford (1976), and Smith et al. (1985).

These methods, when adapted for use in hair assays, involve the quantification of amino acids extracted from the hair fiber. The quantification is performed by a colorimetric chemical reaction between these amino acids and a specific reagent followed by a spectrophotometric reading (Gama 2010; Nogueira 2003; Silva et al. 2004; Sá Dias et al. 2008; Fernandez et al. 2011).

Scanning Electronic Microscopy (SEM)

The SEM's operating principle is the emission of electron beams by a negative electrode by applying a potential difference. The variation in voltage allows the variation of the acceleration of electrons and heats the electrode. The high-energy electron beam hits and interacts on the sample's surface under vacuum condition, and part of the beam is reflected (backscattered and secondary electrons), creating the image. Therefore, the hair sample needs to emit electrons, what is achieved by coating it with vaporized gold to form a thin layer. The emission of X-rays provides information on the chemical composition of the sample (Tomes et al. 2007).

This technique allows the acquisition of information regarding chemical structure and composition of several samples, being capable of generating high extension and resolution images. When applied to hair assessment, this technique may be used to evaluate general aspect, structural and morphological alterations, topography, and substances deposition on hair surface (Gama 2010; Tomes et al. 2007; Velasco et al. 2009).

One example of this method applied to hair damage assessment was the study performed by Robinson (1976) comparing SEM images of virgin versus chemically modified hair. The author demonstrated that bleached and permed hair is more susceptible to damage (breakage, split ends formation, etc.) when exposed to daily aggressions such as shampoo and brushing.

Atomic Force Microscopy (AFM)

The method is based on the scanning of the sample's surface so as to generate bi- and tridimensional surface topography images. The scanning is performed by a probe formed by a pyramid shape tip (100–200 μm length and diameter lower than 20 nm) integrated to a flexible cantilever. On the upper part of the probe's rod, there is a mirror that reflects the light of a laser beam. The reflected beam passes through a lens and hits a photodetector that measures the variations of position and light intensity that are produced by the cantilever's deflections (Chen 2006).

The interaction force between the tip and the sample's surface makes the cantilever approach or depart. The cantilever's deflections are proportional

to these interaction forces. As the tip scans the sample, the morphology variations along the sample alter these interactions thus causing the deflections. A detector captures these variations, and a computer transforms them into topographic images of the sample surface (Velasco et al. 2009; Chen 2006).

Colorimetry

Damages caused on the hair fiber structure may alter its color (Nogueira 2003; Scanavez et al. 2000). Therefore, the instrumental color measurement allows the verification of damage or protection on hair tresses.

The equipment used for hair color measurement is based on the L*a*b* system recommended by the *Commission Internationale de l'Eclairage*. In this system, the color is expressed as a tridimensional coordinate as expressed on Table 4 (Sarruf 2013; Nakano 2006).

Stress-Strain Assessment

This assay aims at analyzing the damage caused to the hair cortex as well as its protection by cosmetic products. Cortex damages influence hair mechanical properties promoting force (resistance) reduction and stress-strain curve profile alterations.

Table 4 Hair color measurement based on the L*a*b* system recommended by the *Commission Internationale de l'Eclairage*

Coordinate	Meaning	Values
L*	Position on the light-dark axis	L* = 0 indicates totally black
		L* = 100 indicates totally white
a*	Position on the red-green axis	Positive values = closer to red
		Negative values = closer to green
b*	Position on the blue-yellow axis	Positive values = closer to yellow
		Negative values = closer to blue

The typical hair fiber stress-strain curve consists of three main regions: (1) elastic or Hookean, (2) plastic, and (3) post-plastic (Nakano 2006).

In the Hookean region, hair maintains its elastic property. This means that when applying a certain load (stress) to the fiber, it will deform proportionally to this load. This region is located between approximately 0 and 2% strain (elongation) compared to the initial length. The stress resistance in this region is mainly due to hydrogen bonds, which are responsible for stabilizing the alpha-helix. Along the Hookean region, when applying stress to the fiber, the alpha-helix starts to change into beta configuration (Gama 2010; Velasco et al. 2009; Nakano 2006).

In the plastic region (between approximately 2 and 25–30% strain), the fiber elongation increases gradually without a significant increase in the required stress. This alteration is explained by the conversion of the microfibrils' internal structure from alpha-helix to beta-keratin (Velasco et al. 2009; Nakano 2006).

In the post-plastic region (above 30% strain), the elongation is again proportional to the applied stress (load). In this region occurs the fiber breakage (breakage point). The resistance to deformation in this region results from the beta-helix structure, and the fiber is stretched until breaking (Velasco et al. 2009; Nakano 2006).

The stress-strain curve is obtained using a dynamometer or texture analyzer. The fiber is placed between the equipment's claws, and the device exerts a force (load) on the fiber to stretch it under constant standardized speed until breakage (Gama 2010; Sá Dias et al. 2008; Nakano 2006; Jachowicz and Smewing 2007).

There are many factors that influence this assay and must be controlled during the study to assure reproducibility. Some examples are fiber diameter, environmental conditions, and fiber length, among others (Velasco et al. 2009).

Hair Gloss

Hair gloss depends mainly on the cuticle arrangement and is related to the reflection of the light

incident on hair. On non-damaged hair, the cuticles are united forming a plain surface with a higher light reflection and, consequently, more gloss (Gama 2010; Velasco et al. 2009).

Therefore, the measurement of hair gloss informs about damage and repair on the cuticle structure. The lower the gloss value obtained, the bigger the damage promoted on the cuticle.

Hair gloss may be quantified on tresses using the glossmeter equipment. The glossmeter emits light on the sample's surface at a specific incidence angle, and it detects the light beam reflected by the sample at a certain correspondent angle. The reflected light is converted by the equipment into a gloss value given in gloss units (G.U.) (Gama 2010; Velasco et al. 2009).

Combability Assay

The equipment used for the hair combability assay is either a dynamometer or a texture analyzer with combs adapted to their probes. The hair tress is fixed on the equipment's upper claw and is then combed under standardized speed by the probe's comb. The equipment measures the required strength for the combs to pass through the tress. The higher the force required for the comb to pass, the worst the tress's combability (Gama 2010; Sá Dias et al. 2008; Velasco et al. 2009; Jachowicz and Smewing 2007).

Fluorescence Microscopy

The hair fibers are impregnated with the fluorescent dye rhodamine B, used as a marker, which infiltrates the fiber. Then, ultrafine transversal cuts are performed on the fiber, and the sample is placed on a glass slide to be observed on the fluorescence microscope. In the obtained image, the rhodamine inside the fiber appears with a green color (Sant'anna 2000).

This procedure allows the evaluation of the diffusion of substances used in haircare products into the fiber (treated vs. control). When the components penetrate to act inside the fiber, the area impregnated with rhodamine is inferior for the treated samples compared with the control.

Evaluation by Image Analysis

This assay involves image capturing of hair tresses under standardized conditions before and after treatment application. The images are then treated with image analysis software to measure parameters such as frizz, volume, and curve maintenance, among others to prove cosmetic products' efficacy and compare treatments (Textile Research Institute 2009).

Assessment of Hair Loss by Breakage

This assessment consists in counting the number of hair fibers that break during repeated standardized brushings. The system promotes repeated brushings on the hair tresses with standardized speed and repetitions concomitant to drying with a hair drier at a fixed distance. The number of broken fibers is then counted manually (Textile Research Institute 2009).

Subjective Assessment (Saloon Test and Cosmetic Appreciability)

These tests involve the questioning of the opinion either of a volunteers panel (cosmetic appreciability) or of a professional hairdresser (saloon test). The subjective efficacy evaluation of the test product is performed simulating real usage conditions by the final consumer (Velasco et al. 2009).

Take-Home Messages

- Hair is a protein filament that grows from follicles of the skin, varies widely across different cultures, but also used to indicate a person personal beliefs or social position, such as age, sex, or religion.

- Cosmetic procedures on hair have an impact on the chemical structure of the hair fiber.
- There are means of preventing hair damage and treating it after it has occurred.
- Preventing hair damage by using products and cosmetic procedures correctly is the best way to keep healthy hair.
- Once the hair fiber is damage, there is no reliable means of repair.

Cross-References

- ▶ Cosmetic Approach for Healthy and Damaged Nails
- ▶ Skin Anatomy, Histology, and Physiology

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Cosmetic Approach for Healthy and Damaged Nails

Robertha Nakamura and Renata Brandão Villa Verde

Abstract

Nowadays, nail care is an important concern for the population. Therefore, the dermatologist needs to know the desired and adverse effects of onychocosmeceutical, because they are increasingly being used by the population. This chapter will discuss the nail beautification and nail care professionals, different types of nail polish, nail polish removers, cuticle removers and softeners, moisturizers for nails, stretchers nail, and oral vitamins used for nails.

Keywords

Nail • Cosmeceutical • Health care • Nail diseases

Contents

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Introduction

The beauty of the nails is defined by the shape, size, brightness, uniform surface, and consistency of the nail plate and depends on the integrity of the matrix and nail bed, periungual tissue, and the entire fingertip (Haneke 2006). Nail care is a social habit. In the United States, 53.815 nail salons, on average, had been accounted in 2014, with two manicurists in a salon (Nails 2014). In 2013, research in England concluded that each year the British woman spends 450 pounds with her nail (http://www.dailymail.co.uk/femail/article-2297649/British-women-spend-450-YEAR-nails.html). In Brazil, for example, it is estimated that in large cities there are 20 salons with manicures and pedicures, by neighborhood (Baran et al. 2011). A survey by the National Association of Commerce of Personal Hygiene Articles and Beauty in 2011 confirmed 550,000 salons in Brazil (Costa et al. 2012). Many women to maintain their self-esteem need to provide healthy and clean nails.

The cosmetic industry increasingly sells onychocosmeceuticals, which enhance the

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appearance of nails. These are cosmetic products containing active ingredients that influence the biological function of the nail. They have therapeutic properties and can be used in cases of nail dystrophies, whose function is to keep the nail healthy and improve its appearance. The desired effect of the use of these products is often not immediately seen because it depends on nail growth, which relies on a number of factors, such as the blood supply, age, temperature, intensity of mobilization, dominance of the respective hand, and hereditary factors (Haneke 2006).

The use of onychocosmeceuticals incorrectly and improperly, as well as the individual sensitivity, may result in onychodystrophy. Many women use nail cosmetics without adverse consequences, but if it occurs, it is important to recognize the causes. The key to avoiding problems with nail cosmetics is prevention through education. It is important that professionals working with nails advise on the care of the nail plate, cuticle, and periungual tissue, thus avoiding trauma and opening a portal of entry for many types of infections.

The aim of this chapter is to discuss the cosmetics and cosmeceuticals nail treatment, its basic components, use, and adverse effects.

Onychocosmeceuticals

Professionals for the Care and Embellishment of the Nails: Manicure, Pedicure, and Podiatrist

Manicure and pedicure provide care for the fingernails and toenails, which focus on embellishment through artistic techniques (Draelos 2000) They use specific materials, such as cutters, pliers, abrasive strips, creams, nail polish, and stretchers. A podiatrist is a technician specialized in caring for the health of the feet and nails and is able to recognize the pathologies of these regions. Your technical management can contribute to the regression of a disease at an early stage. He has the discernment between healthy and pathological, being a professional who works in partnership with physicians.

The maintenance of a healthy nail includes physiological cut in accordance with patterns of good aesthetic appearance. Ideally, the nail plate must be trimmed with as slight a curve as possible and the corners left intact. Many individuals prefer sanding nails frequently to prevent cracking of the cutting force. This technique is especially important when trimming toenails to prevent ingrown nails. These are more common in the feet because of the use of ill-fitting shoes or trauma during physical activity (Draelos 2000; Draelos et al. 2009; Iorizzo et al. 2007).

The cuticles can be pushed proximally and must be left uncut. Unfortunately the cuticle is considered unattractive by most manicures and pedicures because it hinders the uniform application of nail polish. Cuticle removal and vigorous cleansing of hyponychium precipitate the following changes: cuticle trauma, paronychia, onychomycosis, onychobacteriosis, and onychodystrophy, such as Beau's lines (Table 1) (Draelos 2000; Draelos et al. 2009; Iorizzo et al. 2007).

Other problems associated with manicures and pedicures are spread of wart virus by using abrasive strips in lesions, transmission of infectious diseases by improperly sterilized material, and mycobacterial infections (Table 1) (Iorizzo et al. 2007; Chang et al. 2007).

Nail Polish (Enamel, Varnish)

Cosmetic and Beautification: Nail Polish

Nail polish basically consists of pigments suspended in a volatile solvent where film formers are added. Basecoat, nail polish, and topcoat have similar composition.

The basecoat has a function of homogenizing the surface of the nail plate and increasing the adhesion of the nail polish to prevent it from peeling easily. It is primarily composed by film formers and resins (Draelos et al. 2009). The nail polish is mainly composed of a pigment, ensuring the color. And the topcoat adds shine and resistance because it contains high amounts of film formers and plasticizers (Draelos et al. 2009) (Fig. 1).

The nail polish also acts as a physical barrier which prevents direct contact of chemicals and aggression of ultraviolet rays that can penetrate a

Table 1 Nail cosmetic problems, causes, and management (Chang et al. 2007)

Nail cosmetic problem	Cause	Management
Acute bacterial paronychia	Cutting and trauma of cuticle	Not cut or injure the cuticle
Brittle nails	Use of chemicals, solvents, and excessive exposure to water	Avoid contact with chemicals, solvents, and water
Chronic paronychia and loss of cuticle	Cuticle cut, contact with irritants, water, and microorganisms	Protect the cuticle, use of antifungal drug and topical steroids
Fungal transmission	Contaminated material	Sterilization of material
Onycholysis	Long artificial nails, primary irritant reaction	Keep short artificial nails, nail not use as a tool, avoid contact with irritants
Contact dermatitis	Acrylates, formaldehyde, toluene sulfonamide formaldehyde resin	Topical steroids, topical calcineurin inhibitors, emollients, oral antihistamines, phototherapy, avoid contact with triggers
Atypical mycobacterial infection	Improper cleaning of pedicure spas (filter)	Culture-specific antibiotics
Fracturing nail plate	Long and rigid artificial nails	Keep short and thin artificial nails, flexible

Fig. 1 Cosmetic nail polish – pigments suspended in a volatile solvent where film formers are added

nail plate of small thickness. Furthermore, evaporation of water decreases, increasing the moisture and flexibility of the nail plate (Iorizzo et al. 2007).

Most of the enamel is a mixture of different components:

- Film formers (15%): the most frequent of these is the nitrocellulose, a waterproof and non-sensitizing component, which forms a bright and adherent film to the nail plate and gives hardness, abrasion resistance, and viscosity (Draelos et al. 2009; Iorizzo et al. 2007).
- Thermoplastic resin (7%): toluene sulfonamide formaldehyde resin (TSFR) is the most frequent, allows adhesion between the nail plate and the nail polish, and improves gloss and hardness (Iorizzo et al. 2007).

- Plasticizer (7%): usually dibutyl phthalate and camphor, which improve flexibility and prevent retraction (Iorizzo et al. 2007).
- Solvent (70%): toluene, butyl or ethyl acetate, and isopropyl alcohol, which allow the other components of the polish to remain liquids, make a homogeneous viscous preparation, and regulate drying time (Iorizzo et al. 2007).
- Pigment (0–1%): should be resistant to light and produce a good gloss (Iorizzo et al. 2007).
- Other components, not always included: suspending agents, opacifying agents, UV absorbers, and perfume (Draelos et al. 2009; Iorizzo et al. 2007).

The nitrocellulose, a film former, is durable and nontoxic, adheres well to the nail plate, and allows gas exchange, an important factor for the health of the nail. Resins and plasticizers are added in order to increase the flexibility of nail polish (Draelos 2000; Draelos et al. 2009).

The variety in nail polish color is through the addition of organic dyes certified by health agencies or inorganic, containing low amounts of heavy metals (Draelos et al. 2009).

Nail enamels may also contain metal beads to assist in the dispersion of the products prior to application. These beads contain nickel, and sensitivity to nickel may occur with the use of these enamels.

The sensitizing substances found in nail polish can produce allergic contact dermatitis reactions or contact dermatitis by primary irritant (Table 1).

Allergic contact dermatitis is an antigen-specific immune response and once sensitized a reaction will always occur when in contact with the substance. It affects approximately 1–3% of the population. Sensitization occurs by contact of the product with the periungual skin, and difficultly the sensitization occurs through the nail plate. One way to avoid the sensitization is to protect the skin around the nails before using the nail polish. The nail and periungual manifestations of allergic contact dermatitis are yellow discoloration, onychoschizia and granulations in the surface of the nail plate, brittle nails, onycholysis, paronychia, Beau's lines, onychomadesis, abnormal formation of the cuticle, subungual keratosis, and periungual fissures. Reactions can also be a distance, by-product transfer to other regions of the body, especially the eyelids, lower face, and side of the neck, usually with symmetrical involvement. The main source of allergic contact dermatitis is the toluene sulfonamide formaldehyde resin (TSFR), a thermoplastic resin most commonly used in nail enamel. If the patient has presented signs and symptoms suggestive of allergic contact dermatitis with enamel, he/she must do an allergic patch test. This test measures the chemical to which the individual is sensitive and allows to ward off contact. The North American Contact Dermatitis Group found that 4% of the positive results of the patch test were due to TSFR (Iorizzo et al. 2007).

On the other hand, contact dermatitis by primary irritant is common and may occur in any individual, depending on the concentration of the substance and contact time. In this process no immunologic mechanism is involved. The clinical features of primary irritant reaction are eczema of the hands, around the nails, change in the formation of cuticles, onycholysis, and subungual keratosis. It is a common secondary infection (Fig. 3).

Some components of the nail polish, such as formaldehyde, toluene, and dibutyl phthalate, can be considered carcinogenic depending on the exposure quantity and quality. In 2013 the regulation on classification, labeling, and packing of the European Commission officially classified the formaldehyde as a carcinogen. But the EU Commission's Scientific Committee on Consumer Safety has confirmed that formaldehyde is safe for use in cosmetic products at a maximum concentration of 2.2% (www.chemicalwatch.com 2014).

Other dermatological problems associated with nail polish include discoloration of the nail plate, which is seen due to use of pigments dissolved in nail polish instead of pigments in suspension and is more common in red nail polish (Draelos 2000). The nail plate becomes reddish or yellowish due to keratin staining, after continuous use of pigmented nail polish for more than 7 days. The staining fades without treatment after removal and discontinuation of enamel due to

Fig. 2 Dermatological problems associated with nail polish – (**a**) yellow discoloration. (**b**) Onychoschizia, onycholysis. (**c**) Paronychia. (**d**) Granulations in the surface of the nail plate

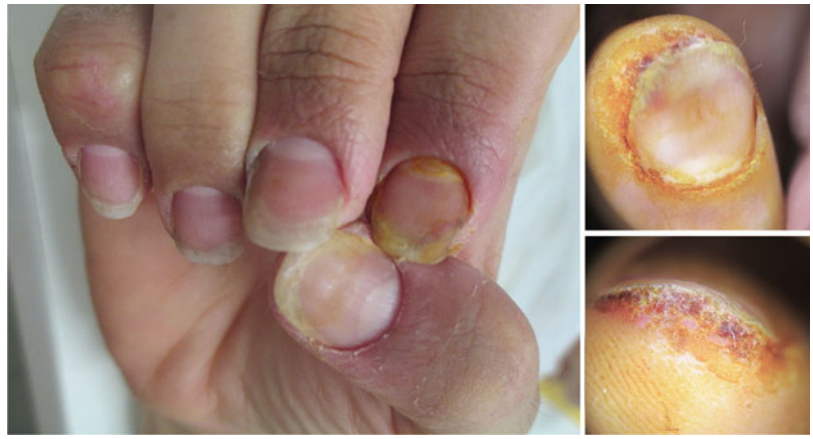

Fig. 3 The clinical features of primary irritant reaction. (**a**) Eczema around the nails, no formation of cuticles, onycholysis. (**b**) Eczema around the nails. (**c**) Subungual keratosis

physiological exchange in the nail plate. It can be prevented with the application of a basecoat (Draelos 2000; Iorizzo et al. 2007).

Nail keratin granulations (superficial, fine, and scaling white spots) and pseudo leukonychia can be observed in women who are used to applying new layer of nail polish over the old one, without using the nail polish remover (Iorizzo et al. 2007) (Fig. 2).

Hypoallergenic Nail Polish

The hypoallergenic nail polish is characterized by replacing the main sensitizers, without leaving the nail polish losing its characteristics. They are divided into three, four, five free, depending on the elements that are not present. The three free are those who lack three substances commonly used in nail polish for its core functions:

1. Toluene: fixation and quick drying
2. Formaldehyde: adhesion and durability of the enamel and hardening of the nail plate
3. Dibutyl phthalate: flexibility, durability, and increased gloss

The four- and five-free nail polish, besides the already mentioned substances, has no formaldehyde resin and camphor, which also are sensitizers (www.nailberry.co.uk/our-philosophy; www.pritinyc.com/PRITINYC-INGREDIENT-LISTINGS-_c_74.html). These enamels make use of polyester resin, phthalic polyester, or cellulose acetate butyrate, decreasing the chances of allergy. But the sensitivity is still possible (www.pritinyc.com/PRITINYC-INGREDIENT-LISTINGS-_c_74.html).

Gel Nail Polish

It was recently introduced as the nail gel system, which has the same components of the cosmetic nail polish but is more resistant to day-to-day activities and has greater durability. The gel covers the entire nail plate and then is photopolymerized and dried in contact with UV light or LED. To use the gel, it is necessary to have a specific drying equipment. The LED cabin takes 60 s to dry the nails and UV takes 3 min. Removal is difficult and used products can damage nails (CND Shellac™ Application and Removal 2011).

Vegan Nail Polish

Vegan nail polishes are natural formulas, an ecological alternative with a tendency to preserve the vitality of the nails. These formulas are nontoxic nail polish. They are presented in the form of film or water-based with penetration through the nail plate and uniform release of component. They are generally used for treating brittle nails or used as a trend, associating aesthetic and safety. These products are not contraindicated in pregnant women and children. Its components are mostly natural moisturizers as silica, oils, and vitamin E (http://nailsmag.epubxp.com/i/472189-apr-2015/132).

Nail Hardeners and Nail Strengtheners

The thin nails, that fold easily, are soft and require hardeners. The nails that break but are not smooth need strengtheners. They are generally used as a basecoat (Iorizzo et al. 2007).

Those products are a modification of nail polish with the addition of various substances such as keratin, vitamins, calcium fluoride, natural oils, natural fibers, nylon fibers, Teflon, and silk. Most nail strengtheners available on the market have 1–2% formaldehyde, substances which permanently alter the structure of the nail plate by cross-linking of keratin, thus promoting one hard plate with decreased flexibility. The same occurs with products based on aluminum at 5% in propylene glycol. Acetates, toluene, nitrocellulose, acrylic, and polyamide resins are used for structural reinforcement of the ungual plate (http://nailsmag.epubxp.com/i/472189-apr-2015/132). Some products contain 1% nylon fibers and are known as nail hardeners. Other strengthener additives include hydrolyzed proteins, modified vegetable extracts, glycerin, propylene glycol, and metal salts (Draelo et al. 2009).

The prolonged use of nail hardeners may paradoxically cause brittle nails, since the cross-link density rises over time and the flexibility is reduced (Dimitris and Ralph 2012). The need for periodic removal of those products can also contribute to the nail fragility, due to dryness caused by nail polish remover (Iorizzo et al. 2007).

Formaldehyde is allowed for use as nail hardener in a concentration of up to 2%. The most used concentration is 1%, with the lower risk of allergic

contact dermatitis. There is a restriction tendency of formaldehyde use after the Food and Drug Administration (FDA) warning. This considered the formaldehyde as a possible carcinogen agent according to the quantity and quality used. Products containing formaldehyde must make clear the existence of the compound and its concentration on the label (http://www.fda.gov/Cosmetics/ProductsIngredients/Products/ucm127068.htm#ingred).

Other adverse effects to the use of formaldehyde include allergic contact dermatitis, contact dermatitis by primary irritant, paronychia, onycholysis, subungual keratosis, subungual hemorrhage, blue discoloration of the nail plate, and throbbing pain , as well as dryness of the nail plate and periungual region (Draelos et al. 2009; Iorizzo et al. 2007).

Fillers Nail Polish

Enamels are used mainly for striated nails in order to fill and level the surface of the nail plate. The components of this nail polish are nylon fibers and acrylates. They leave the uniform surface however rough. Many of these have a smooth enamel for finishing (Baran et al. 2011).

Adhesive Nail Polish (Stick-On Nail Dressings)

Adhesive nail polish is a self-adherent and colored plastic film that can be fixed to the nail plate. After removing the film, the nail plate can appear thin and fragile. The final cosmetic effect is poor (Iorizzo et al. 2007).

Water-Soluble Enamels

The water-soluble enamels are widely used as onychocosmeceuticals to improve the moisture and reduce the peeling of the nail plate. The most commonly used substances are rich in organic silica such as Nonychosine and more recently *Equisetum arvense*.

Formulations based on *Equisetum arvense* (medicinal extract) and methylsulfonylmethane (sulfur donors) in aqueous solution are part of the new technology based on the use of chitosan derivatives as film formers and as vehicle for active substances for the nail (Sparavigna et al. 2006).

The *Equisetum arvense* is an organic silica source and works on strengthening and stiffening the nail. The hydroxypropyl chitosan (HPCH) is an invisible film-forming agent, with high plasticity and affinity for keratin. It is an excellent carrier of active substances and improves moisture of the nail. The sulfur donor stabilizes the nail plate acting in disulphide bonds, increases the quality of the nail plate, and aids in nail growth (Sparavigna et al. 2006).

This product must be applied once a day, at night, on dry nails. The hands cannot be washed for at least 6 h because it is a water-soluble product. There is no consensus on the time of use, but the results begin to be noticed after 2 weeks. It is recommended to use a minimum of 12 weeks.

There are studies demonstrating significant decrease in onychoschizia and nail fragility, improving the appearance of the nail. Onycholysis, onychorrexis, and thinning of the nail plate showed no improvement with this treatment.

Nail Polish Removers

The nail polish removers contain solvents such as acetone, alcohol, ethyl acetate, or butyl acetate. Some removers contain greasy substances, such as cetyl alcohol, cetyl palmitate, lanolin, castor oil, and other synthetic oils. The dryness of the nail plate can be due to constant use of remover containing acetone. The current trend is the use of free acetone removers that use other solvents such as ethyl acetate, emollients, and oils that dry less the nail plate. Oils increase water evaporation time, so they are accepted as occlusive moisturizers with less efficacy compared to the other solvents (Draelos et al. 2009).

The remover can irritate the periungual region and also contribute to the fragility of the nail plate, developed with dry nails, brittle, onychoschizia, and leukonychia (Table 1).

Cuticle Removers and Softeners

The cuticle plays an important protective role against bacterial and fungal infections. It should

not be removed, but it often happens because of adornment and beautification process of the nails adopted by many women around the world. Removal of cuticle is performed mechanically or chemically, with the risk of predisposition to such infections.

The cuticle removers act by destruction of keratin, by breaking the bridges of cystine. They are formed by association of alkaline substances in liquid or cream base. Sodium hydroxide and potassium hydroxide (2–5%) are the main alkalis used. The humectants such as glycerin and propylene glycol can be added to reduce the irritation and evaporation of water and to increase viscosity. However, they can damage the nail plate because of softening and super moisturizing. Prolonged exposure to these caustic substances can cause contact dermatitis for primary irritant (Draelos et al. 2009).

There are milder formulations, but less effective, containing inorganic salts of trisodium phosphate or tetrasodium pyrophosphate. Organic bases such as trolamine (trielanolamina) may also be used (Draelos et al. 2009).

Another product used in this category, known as softener cuticle, is composed of quaternary ammonium (3–5%). It is sometimes associated with urea 20%, lactic acid 10%, and salicylic acid. The purpose is to soften the protein to push the cuticle and facilitate the mechanical removal. There is a risk of contact dermatitis, burning, and irritation in sensitive individuals. Wounds and fissures in the periungual region can burn when in contact with the cuticle softeners (Draelos et al. 2009).

Moisturizers for Nails

They are creams and lotions that act as occlusive substances. The petrolatum or lanolin and humectants such as glycerin and propylene glycol are most commonly used. A variety of other substances with proteins, fluorides (ammonium hexafluorophosphate), and silicium are included in the preparations. The addition of alpha hydroxy acids, lactic acid, and urea increases the water-binding capacity of the nail plate and on the other hand may cause contact dermatitis (Draelos et al. 2009; Iorizzo et al. 2007).

Another way to moisturize the nails is through the oils: jojoba oil, panthenol, bisabolol, vitamins, and amino acids. It is not clear what role the vitamins play on the nails. Some oils can help to hold humidity, make the nail more elastic, and thus prevent nail split (Haneke 2006).

Moisturizers for nails are for dry, brittle, scaly, and cracked nail plates. It works better if applied under occlusion, preferably at night for at least 3 months. It acts even better if the nails are underwater in warm water for 10–20 min before application of moisturizers (Draelos et al. 2009). It is essential to stop activities that contribute to the dryness of nails, such as frequent contact with water, detergents, solvents, or nail polish remover.

Stretchers Nail

Artificial Nails

Artificial nails are preformed plastic nails that are glued onto the natural nail. The glue is ethyl cyanoacrylate, a sensitizer that may cause allergic contact dermatitis. For this reason they should not be worn more than 48 h each time. This glue can also be used to repair a nail with distal or transverse slot, gluing plastic film strips, paper, or cotton. Fiber glass strips are also used as extenders or to occlude the slots (Draelos et al. 2009; Iorizzo et al. 2007).

Sculptured Nails

Sculptured nails are formed onto the natural nail and for this reason have a more natural aspect. They can be porcelain, gel, and acrylic. The removal of these can be made by soaking in acetone. Otherwise they will be removed with the growth of the nail (Draelos 2000).

The acrylic nails are created with combination of monomer liquid (liquid ethyl or isobutyl methacrylate) and powdered polymer (polymethyl methacrylate). Take shape after the polymerization phenomenon, chemical reaction between the two components, or after use of organic accelerators such as benzoyl peroxide (Draelos 2000).

Fig. 4 Sculptured nails (acrylic nails). (**a**) Combination of monomer liquid and powdered polymer. (**b**) The gel nails are a mixture of ethyl cyanoacrylate and polymethyl methacrylate monomers. (**b**) LED cabin for polymerization and hardening. (**c**) Aesthetic appearance

These products are sensitizers and can cause allergic contact dermatitis (Iorizzo et al. 2007). In addition, the monomers can cause irritating reactions, manifested as subungual keratosis with or without onycholysis (Draelos 2000).

The gel nails are a mixture of ethyl cyanoacrylate and polymethyl methacrylate monomers. They require UV radiation for polymerization and hardening. Hypoallergenic gel nails do not contain methacrylic acid but may still cause contact dermatitis because they contain other sensitizers (Iorizzo et al. 2007).

Many people are not aware that sculptured nails require more care than natural nails. The acrylic of the edges is lost with continued use of sculptured nails. The free edges must be cut, and new acrylic should be placed every 3 weeks, thus preventing the development of an environment for infection. Sculptured nails move up with the growth of the natural nail, so more polymer should be added at proximal region. This procedure is known as extra filler (Iorizzo et al. 2007) (Fig. 4).

Photo-Glued Nails

It is a variant of sculptured nails, formed from a sculpted acrylic onto the nail plate, which needs to be exposed to magnesium light for 1–2 min to dry. This technique is similar to dental restoration (Iorizzo et al. 2007).

Its use is being discontinued because of adverse effects: photo-onycholysis and paresthesia.

The adverse effects caused by artificial nails in general are periungual and subungual itching, pain, paresthesia, eczematous reaction, onycholysis, paronychia, temporary or permanent nail loss, contact dermatitis in distant sites, subungual keratosis, and increased susceptibility to onychomycosis. The traumatic removal of these can result in onychoschizia and nail pitting (Draelos 2000). It has also been noted that the natural nail comes thin, brittle, and dry after application of sculptured nails (Chang et al. 2007) (Fig. 5).

Oral Vitamins

Biotin

Biotin, also called hair and nail vitamin, is a water-soluble B complex vitamin. It is necessary as a coenzyme for carboxylation metabolic reactions: gluconeogenesis, fatty acid synthesis, nucleic acid synthesis, and amino acid catabolism (Scheinfeld et al. 2007). It also stimulates epidermal differentiation and increases the keratin

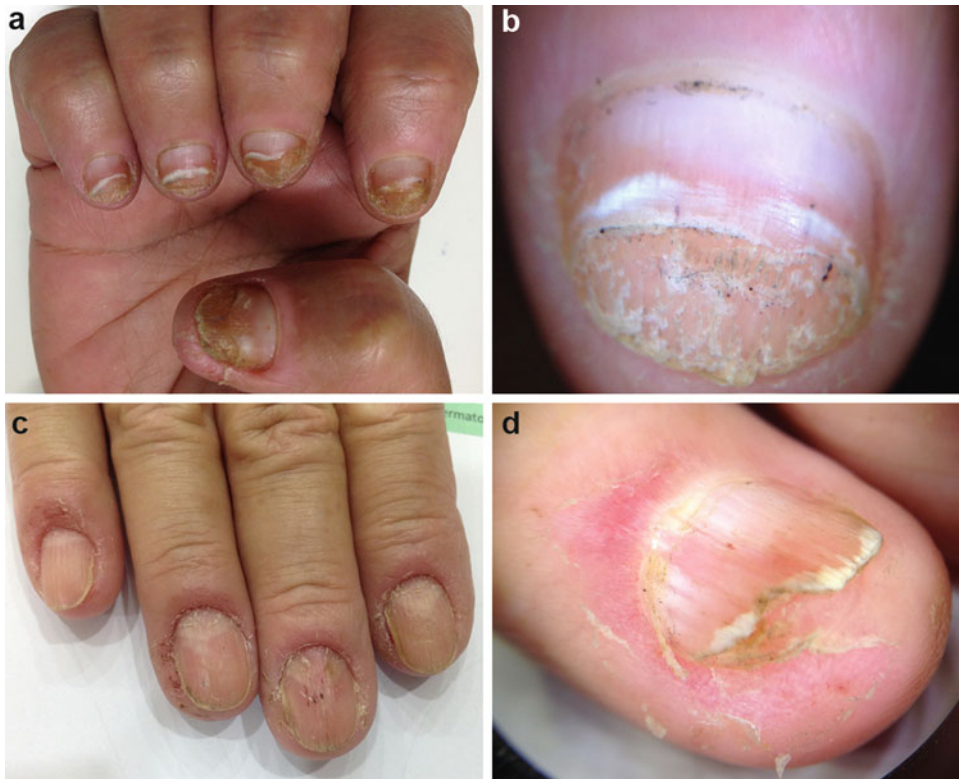

Fig. 5 The adverse effects caused by artificial nails. (**a**) Subungual eczematous reaction. (**b**) Temporary distal nail loss, subungual keratosis. (**c**) Periungual eczematous reaction, paronychia. (**d**) Periungual and subungual eczematous reaction, paronychia, temporary distal nail loss

synthesis, resulting in increased growth rate of the nail plate and improvement of brittle nails. Its main source is synthesized by intestinal bacteria, because the food source has low bioavailability (Nisbett 2002).

The dose of food supplementation is done per microgram ranging from 10 to 30 mcg (Scheinfeld et al. 2007). The therapeutic dose varies from 2.5 to 10 mg per day (Haneke 2006). The effects of biotin are increased thickness, hardness, and growth of the nail plate and are seen after 2–3 months of use. There was no evidence of toxicity at doses up to 200 mg daily (Nisbett 2002).

Pyridoxine

A combination of pyridoxine 25–30 mg and ascorbic acid was recommended for brittle nails, but there is a lack of scientific evidence of their effectiveness (Haneke 2006).

Vitamin E

Vitamin E, a known antioxidant, has been given in the yellow nail syndrome with some success. No beneficial effect on brittle nail is documented (Haneke 2006; Iorizzo et al. 2007).

Iron and Zinc

Iron and zinc deficiencies can cause brittle nails. Supplementation of these elements, even without a demonstrable deficiency, causes an improvement in nail fragility (Haneke 2006). Iron supplementation should only be made if ferritin levels are less than 10 ng/ml (Iorizzo et al. 2007).

Silicium

Silicium plays a role in the synthesis of glycosaminoglycans and collagen type 1. It is one of the nail components in a proportion of one to ten parts per million (Nails Magazine 2014–2015).

Silicium favors the cross-linking of keratin, ensuring firmness and resistance of the nail plate, and is being used for brittle nails (Haneke 2006). Choline-stabilized orthosilicic acid (ch-OSA) is a bioavailable form of silicium (Barel et al. 2005).

Cystine

Cystine is an amino acid disulfide, which makes the connection between two keratin chains. It could be useful in promoting nail growth and its hardness (Iorizzo et al. 2007).

Conclusion

We conclude this chapter by suggesting the dermatologist becomes familiar with onychocosmeceutical. He must stay current with the trends at beautification of the nails, keeping in mind its palliative effect, and must be able to recognize the possible adverse effects as the various onychodystrophy, the allergic contact dermatitis, and dermatitis for primary irritant.

Take Home Messages

- The maintenance of a healthy nail includes physiological cut, to avoid ingrown nails.
- The cuticles can be pushed proximally and must be left uncut to prevent paronychia and other dystrophies.
- The nail polish acts as a physical barrier and its main adverse effect is contact dermatitis.
- Most nail strengtheners available on the market have 1–2% formaldehyde.
- The *Equisetum arvense* is an organic silica source and works on strengthening and stiffening the nail.
- Nail polish removers containing acetone cause drying of the nail plate.
- Moisturizers for nails are for dry, brittle, scaly, and cracked nail plates.
- Artificial nails have main adverse effects such as contact dermatitis and, moreover, may result in onychodystrophy.
- Oral vitamins with more scientific evidence for use in brittle nails are biotin and silicium, in addition to iron and zinc supplementation.
- Care is required in relation to the adverse effects of any substance used for adornment and for nail care.

Cross-References

- ▶ Cosmetic Approach for Healthy and Damaged Hair
- ▶ Skin Anatomy, Histology, and Physiology

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